IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC Plaintiff, v. TEVA PHARMACEUTICALS USA and TEVA PHARMACEUTICAL INDUSTRIES LTD. Defendants.	)	Civil Action No. 06-89-GMS

DECLARATION OF DANIEL C. MULVENY, ESQ. IN SUPPORT OF PLAINTIFF PFIZER INC'S OPENING BRIEF IN SUPPORT OF ITS CONTINGENT MOTION TO ENJOIN THE TEVA DEFENDANTS FROM PROCEEDING WITH THEIR LATER-FILED SUIT IN THE SOUTHERN DISTRICT OF NEW YORK

I, Daniel C. Mulveny Esq., hereby declare as follows.

1. I am an attorney with Connolly Bove Lodge & Hutz LLP, counsel of record for Plaintiff Pfizer Inc ("Pfizer") in this action. I make this declaration in support of plaintiff Pfizer Inc's opening brief in support of plaintiff Pfizer Inc's contingent motion to enjoin the Teva defendants from proceeding with their later-filed suit in the Southern District Of New York.

2. Connolly Bove Lodge & Hutz LLP is counsel of record in *Pfizer Inc v. Sandoz Inc. et al.* 1:06-cv-00090-JJF, which is pending in the United States District Court for the District of Delaware. A true and correct copy of the complaint in that action (without exhibits), which was filed on February 8, 2006, is attached hereto as Exhibit A.

3. On February 16, 2006, Pfizer alerted the Court about the pendency of the instant action and the *Pfizer Inc v. Sandoz Inc. et al.*, 1:06-cv-00090-JJF action and their separate judge

assignments. A true and correct copy of the letter to the Court in the *Pfizer Inc v. Sandoz Inc. et al.*, 1:06-cv-00090-JJF action is attached hereto as Exhibit B.

4. Connolly Bove Lodge & Hutz LLP is counsel of record in *Teva Pharmaceuticals USA Inc. et al. v. Pfizer Inc*, 06cv1134 (LAP) (the "Teva DJ Action"), which defendants', Teva Pharmaceuticals USA and Teva Pharmaceutical Industries Ltd. (respectively "Teva USA" and "Teva Ltd."; collectively "Teva") filed on February 14, 2006, in the United States District Court for the Southern District of New York six days after Pfizer brought the instant action in this Court. A true and correct copy of Teva's complaint in the Teva DJ Action (without exhibits) is attached hereto as Exhibit C.

5. Attached hereto as Exhibit D is a true and correct copy (without exhibits) of Pfizer's Answer and Counterclaims in *Teva Pharmaceuticals USA Inc. et al. v. Pfizer Inc*, 06cv1134 (LAP) which was filed on March 7, 2006.

6. Attached hereto as Exhibit E is a true and correct copy of U.S. Patent No. 6,268,489.

7. Attached hereto as Exhibit F is a true and correct copy of U.S. Patent No. 5,605,889.

8. Attached hereto as Exhibit G is a true and correct copy of a printout from LexisNexis Courtlink showing all of the District of Delaware cases since 1998 where Teva USA and/or Teva Ltd. has been a party.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Executed at Wilmington, Delaware, on March 8, 2006.

Daniel C. Mulveny, Esq. (#3984)
CONNOLLY BOVE LODGE & HUTZ LLP
The Nemours Building
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899
(302) 658-9141

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CERTIFICATE OF SERVICE

I hereby certify that on March 9, 2006, I electronically filed **DECLARATION OF DANIEL C. MULVENY, ESQ. IN SUPPORT OF PLAINTIFF PFIZER INC'S OPENING BRIEF IN SUPPORT OF ITS CONTINGENT MOTION TO ENJOIN THE TEVA DEFENDANTS FROM PROCEEDING WITH THEIR LATER-FILED SUIT IN THE SOUTHERN DISTRICT OF NEW YORK** with the Clerk of Court using CM/ECF which will send notification of such filing to the following:

Mary B. Matterer
Morris James Hitchens & Williams LLP
222 Delaware Avenue, 10th Floor
P.O. Box 2306
Wilmington, DE 19899-2306

I hereby certify that on March 9, 2006, I have mailed by First Class Mail, the document(s) to the following non-registered participants:

Steven Lee
Elizabeth J. Holland
Sheila Mortazavi
Cynthia Lambert Hardman
Kenyon & Kenyon LLP
One Broadway
New York, NY 10004

/s/ Rudolf E. Hutz
Rudolf E. Hutz (#484)
Daniel C. Mulveny (#3984)
1007 N. Orange Street
P. O. Box 2207
Wilmington, DE 19899-2207
(302) 658-9141
Attorneys for Pfizer Inc

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC Plaintiff, v. SANDOZ INC. and NOVARTIS AG Defendants.	)	Civil Action No. 06 90

COMPLAINT

Plaintiff Pfizer Inc ("Pfizer") by its attorneys, for its Complaint of patent infringement against Defendants Sandoz Inc. and Novartis AG (collectively referred to as "Sandoz"), alleges as follows:

PARTIES

1. Pfizer is a corporation organized and existing under the laws of the State of Delaware and has corporate offices at 235 East 42nd Street, New York, New York 10017.

2. Pfizer holds approved New Drug Application No. 050711 for azithromycin tablets for oral administration, 250 mg, which it sells under the registered name ZITHROMAX.

3. Pfizer holds approved New Drug Application No. 050784 for azithromycin tablets for oral administration, 500 mg, which it sells under the registered name ZITHROMAX.

4. Pfizer holds approved New Drug Application No. 050730 for azithromycin tablets for oral administration, 600 mg, which it sells under the registered name ZITHROMAX.

5. Pfizer also holds approved New Drug Application No. 050710 for azithromycin in an oral suspension (100 mg base/5ml and 200mg base/5 ml); approved New Drug Application No. 050693 for azithromycin in an oral suspension (1 gram base/packet); and approved New Drug Application No. 050733 for azithromycin in injectable form (500 mg base/vial) -- all of which are sold by Pfizer under the registered name ZITHROMAX.

6. On information and belief, defendant Sandoz Inc. is a corporation organized and existing under the laws of the State of Colorado, having its principal place of business at 506 Carnegie Center, Suite 400, Princeton, N.J. 08540 and a manufacturing facility at 2555 West Midway Boulevard, Broomfield, Colorado 80020.

7. On information and belief, defendant Novartis AG is a corporation or other entity organized and existing under the laws of Switzerland, having its principal place of business at Basel, Switzerland. Sandoz Inc. is a wholly-owned subsidiary or division of Novartis AG.

JURISDICTION AND VENUE

8. This action for patent infringement arises under the patent laws of the United States, United States Code, Title 35. This Court has subject matter jurisdiction over this action pursuant to the provisions of United States Code, Title 28, §§ 1331 and 1338(a).

9. Sandoz Inc. is, upon information and belief, transacting business in Delaware. Accordingly, Sandoz Inc. is subject to personal jurisdiction in this District under 10 Del. Code § 3104.

10. Sandoz Inc. is, upon information and belief, also engaged in activities in Delaware that give rise to the cause of action that is the basis for this complaint. Accordingly, Sandoz Inc. is subject to personal jurisdiction in this District under 10 Del. Code § 3104.

11. The activities of Sandoz Inc. that are the basis for this complaint, have been and remain, upon information and belief, under the control and direction of the parent company, Novartis AG. Accordingly, Novartis AG is subject to personal jurisdiction in this District under 10 Del. Code § 3104.

12. Venue is proper in this District pursuant to the provisions of United States Code, Title 28, §§ 1391(c), (d) and 1400(b).

THE PATENT-IN-SUIT

13. On December 20, 2005 the United States Patent and Trademark Office ("USPTO") issued U.S. Patent No. 6,977,243 ("the '243 patent"), entitled "Crystal Forms of Azithromycin", based on an application filed by Zheng J. Li and

Andrew V. Trask and assigned to Pfizer. A true and complete copy of the '243 patent as issued is attached hereto as Exhibit A.

14. Errors appeared in the '243 patent as published on December 20, 2005, as a result of mistakes made by the USPTO.

15. On January 18, 2006, Pfizer filed a Request for Certificate of Correction to correct errors in the '243 patent.

16. On February 7, 2006, a Certificate of Correction of the '243 patent duly and legally issued and a true and complete copy of the Certificate of Correction is attached hereto as Exhibit B. The Certificate of Correction was published and appeared on the United States Patent and Trademark Office website on February 8, 2006.

17. The '243 patent, as corrected by the Certificate of Correction, covers azithromycin sesquihydrate.

18. Since its issue date, plaintiff Pfizer has been and remains the owner of all right, title and interest in and to the '243 patent, including its Certificate of Correction.

COUNT 1
(Patent Infringement)

19. The allegations of paragraphs 1-18 above are repeated and re-alleged as if set forth fully herein.

20. Upon information and belief, on or about November 14, 2005, Sandoz Inc. received approval for Abbreviated New Drug Application ("ANDA") No.

065211 for azythromycin tablets, 250 mg and continues to have such approval.

21. Upon information and belief, on or about November 14, 2005, Sandoz Inc. received approval for ANDA No. 065212 for azythromycin tablets, 500 mg and continues to have such approval.

22. Upon information and belief, on or about November 14, 2005, Sandoz Inc. received approval for ANDA No. 065209 for azythromycin tablets, 600 mg and continues to have such approval.

23. Upon information and belief, Sandoz Inc. began shipping azithromycin tablets, 250 mg, 500 mg and 600 mg, on, about or after November 14, 2005 and continues to do so, including shipments into the State of Delaware.

24. Upon information and belief, the drug products containing azithromycin that were the subject of ANDA Nos. 065211, 065212 and 065209, contain azithromycin sesquihydrate and are covered by one or more claims of the '243 patent.

25. Upon information and belief, the azithromycin tablets, 250 mg, 500 mg and 600 mg, that Sandoz Inc. began shipping on, about or after November 14, 2005, contain azithromycin sesquihydrate and are covered by one or more claims of the '243 patent.

26. Upon information and belief Sandoz Inc. has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065211 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of tablets, 250 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

27. Upon information and belief Sandoz Inc. has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065212 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of tablets, 500 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

28. Upon information and belief Sandoz Inc. has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065209 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of tablets, 600 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

29. Upon information and belief Sandoz Inc. has infringed and continues to infringe one or more claims of the '243 patent under 35 U.S.C. § 271(a) by importing into the United States and offering to sell and selling within the United States a product containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

30. Pfizer will be irreparably harmed if Sandoz Inc. is not enjoined from infringing the '243 patent.

COUNT II
(Active Inducement of Infringement)

31. Pfizer repeats and re-alleges paragraphs 1-30 above as if fully set forth herein.

32. On information and belief, defendant Novartis AG actively participated in the research and development of the azithromycin products which

are the subject of ANDA Nos. 065211, 065212 and 065209 and was responsible for and controlled the preparation, filing and prosecution of these ANDAs.

33. On information and belief, defendant Novartis AG has actively engaged in activities relating to the importation, manufacture, use, sale or offer for sale of the azithromycin tablets, 250 mg, 500 mg and 600 mg that Sandoz Inc. began shipping on, about or after November 14, 2005, and those activities induced Sandoz Inc. to undertake such importation, manufacture, use, sale or offer for sale of the azithromycin tablets whereby Sandoz Inc. directly infringed one or more claims of the '243 patent.

34. Defendant Novartis AG is therefore liable as an infringer of the '243 patent under 35 U.S.C. § 271(b) by actively inducing defendant Sandoz Inc. to directly infringe the '243 patent.

35. Pfizer will be irreparably harmed if Novartis AG is not enjoined from inducing the infringement of the '243 patent.

COUNT III
(Declaratory Judgment of Infringement of the '243 Patent)

36. Pfizer repeats and re-alleges paragraphs 1 through 35 above as if fully set forth herein.

37. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties. Sandoz Inc. has taken immediate and active steps to continue the use, sale and/or offer for sale in the United States, and specifically in the State of Delaware, of the azithromycin

tablets, 250 mg, 500 mg and 600 mg that Sandoz Inc. began shipping on, about or after November 14, 2005.

38. Upon information and belief, Sandoz Inc. intends to offer to sell, sell or use within the United States, and specifically within the State of Delaware, the azithromycin tablets, 250 mg, 500 mg and 600 mg that Sandoz Inc. began shipping on, about or after November 14, 2005, prior to the expiration of the '243 patent.

39. Upon information and belief, Sandoz Inc.'s activities as described in paragraph 38 will infringe the '243 patent under 35 U.S.C. § 271(a).

40. Pfizer will be irreparably harmed if Sandoz Inc. is not enjoined from infringing the '243 patent.

COUNT IV
(Declaratory Judgment of Infringement of the '243 Patent)

41. Pfizer repeats and re-alleges paragraphs 1 through 40 above as if fully set forth herein.

42. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties. Novartis AG has taken immediate and active steps to actively induce Sandoz Inc. to continue the use, sale and/or offer for sale in the United States, and specifically in the State of Delaware, of the azithromycin tablets, 250 mg, 500 mg and 600 mg that Sandoz Inc. began shipping on, about or after November 14, 2005.

43. Upon information and belief, Sandoz Inc. intends to offer to sell, sell or use within the United States, and specifically within the State of Delaware, the

azithromycin tablets, 250 mg, 500 mg and 600 mg that Sandoz Inc. began shipping on, about or after November 14, 2005, prior to the expiration of the '243 patent, and Novartis AG has actively induced Sandoz Inc. to engage in these activities.

44. Upon information and belief, Sandoz Inc.'s activities as described in paragraph 43 will directly infringe the '243 patent under 35 U.S.C. § 271(a). Accordingly, Novartis AG's activities as described in paragraph 43 will infringe the '243 patent under 35 U.S.C. § 271(b).

45. Pfizer will be irreparably harmed if Novartis AG is not enjoined from infringing the '243 patent.

PRAYER FOR RELIEF

WHEREFORE, Pfizer requests the following relief:

A. A judgment under 35 U.S.C. § 271(a) that Sandoz Inc.'s azithromycin product (250 mg tablet), which is marketed under approved ANDA No. 065211, infringes the '243 patent;

B. A judgment under 35 U.S.C. § 271(a) that Sandoz Inc.'s azithromycin product (500 mg tablet), which is marketed under approved ANDA No. 065212, infringes the '243 patent;

C. A judgment under 35 U.S.C. § 271(a) that Sandoz Inc.'s azithromycin product (600 mg tablet), which is marketed under approved ANDA No. 065209, infringes the '243 patent;

D. A judgment under 35 U.S.C. § 271(e)(2)(A) that Sandoz Inc. infringed the '243 patent by submitting ANDA No. 065211 prior to the date of expiration of

the '243 patent;

E. A judgment under 35 U.S.C. § 271(e)(2)(A) that Sandoz Inc. infringed the '243 patent by submitting ANDA No. 065212 prior to the date of expiration of the '243 patent;

F. A judgment under 35 U.S.C. § 271(e)(2)(A) that Sandoz Inc. infringed the '243 patent by submitting ANDA No. 065209 prior to the date of expiration of the '243 patent;

G. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065211 shall be a date not earlier than the date of expiration of the '243 patent;

H. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065212 shall be a date not earlier than the date of expiration of the '243 patent;

I. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065209 shall be a date not earlier than the date of expiration of the '243 patent;

J. A preliminary and permanent injunction enjoining defendant Sandoz Inc. from making, using, selling, offering to sell, or importing a product containing azithromycin sesquihydrate until the date of the expiration of the '243 patent;

K. A judgment under 35 U.S.C. § 271(b) that defendant Novartis AG has actively induced defendant Sandoz Inc. to infringe the '243 patent;

L. A preliminary and permanent injunction enjoining defendant Novartis AG from actively inducing infringement of the '243 patent;

M. A declaratory judgment that Sandoz Inc.'s azithromycin product (250 mg tablet), which is marketed under approved ANDA No. 065211, will infringe the '243 patent;

N. A declaratory judgment that Sandoz Inc.'s azithromycin product (500 mg tablet), which is marketed under approved ANDA No. 065212, will infringe the '243 patent;

O. A declaratory judgment that Sandoz Inc.'s azithromycin product (600 mg tablet), which is marketed under approved ANDA No. 065209, will infringe the '243 patent;

P. A declaratory judgment that defendant Novartis AG will actively induce defendant Sandoz Inc. to infringe the '243 patent;

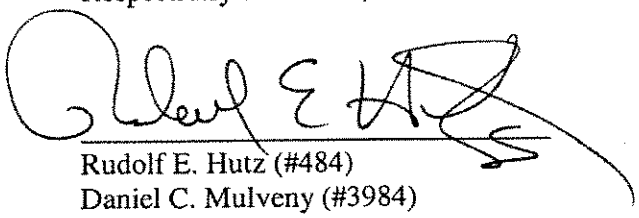
Q. An award of damages to Pfizer as a result of Sandoz's infringement of the '243 patent, altogether with interest and costs pursuant to 35 U.S.C. § 271(e)(4)(C);

R. An award of damages to Pfizer as a result of Sandoz's infringement of the '243 patent, altogether with interest and costs pursuant to 35 U.S.C. §284;

S. A declaration by this Court that this an exceptional case and an order that Sandoz pay to Pfizer its reasonable attorneys' fees, costs and interest in this action, pursuant to 35 U.S.C. § 285; and

T. Such further and other relief as this Court may deem just and proper.

Respectfully submitted,



Dated: February 8, 2006

Rudolf E. Hutz (#484)
Daniel C. Mulveny (#3984)
Connolly Bove Lodge & Hutz LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899-2207
(302) 658-9141
(302) 658-5614 (Facsimile)

Attorneys for Plaintiffs Pfizer,
and Pfizer Global

(445562)

EXHIBIT B

CONNOLLY BOVE LODGE & HUTZ LLP
ATTORNEYS AT LAW

The Nemours Building
1007 North Orange Street
P.O. Box 2207
Wilmington DE 19899
TEL (302) 658 9141
FAX (302) 658 5614

1990 M Street, NW, Suite 800
Washington DC 20036
TEL (202) 331 7111
FAX (202) 293 6229

WEB www.cblh.com

Rudolf E. Hutz
Partner

TEL (302) 888-6266
FAX (302) 656-9072
EMAIL rhutz@cblh.com
REPLY TO Wilmington Office

February 16, 2006

Honorable Joseph J. Farnan, Jr.
U. S. District Court for the
District of Delaware
844 North King Street
Wilmington, DE 19801

Re: Pfizer Inc v. Sandoz Inc. and Novartis AG,
Case 1:06-cv-00090-JJF

Dear Judge Farnan:

We were notified yesterday that the above-captioned case has been assigned to Your Honor. As counsel for Pfizer Inc, I wish to advise that on the same day the complaint was filed in this action, Pfizer filed suit on the same patent against Teva Pharmaceuticals USA and Teva Pharmaceutical Industries Ltd. That case, captioned Pfizer Inc v. Teva Pharmaceuticals USA and Teva Pharmaceutical Industries Ltd., CA 1:06-cv-00089-GMS, has been assigned to Judge Gregory M. Sleet. While the plaintiff and the patent are the same in each action, the defendants and the products at issue are different.

I am also advising Judge Sleet of these circumstances.

Very truly yours,

Rudolf E. Hutz
Connolly Bove Lodge & Hutz LLP

REH.bjh

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EXHIBIT C

06 CV 1134

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.

Plaintiffs,

v.

PFIZER INC.,

Defendant.

Civil Action No.

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd."), for their Complaint against Pfizer Inc. ("Pfizer"), allege on personal belief as to themselves and on information and belief as to the conduct of Pfizer as follows:

THE PARTIES

1. Teva USA is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

2. Teva Ltd. is a corporation organized under the laws of Israel, and maintains its principal place of business at 5 Basel Street, Petach Tikva 49131, Israel.

3. On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.

4. On information and belief, Pfizer owns U.S. Patent No. 6,977,243 ("the '243 patent"), entitled "Crystal Forms of Azithromycin," a copy of which is attached hereto as Exhibit A.

5. On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-711 for ZITHROMAX® 250 mg azithromycin tablets, NDA No. 50-730 for ZITHROMAX® 600 mg azithromycin tablets; and NDA No. 50-784 for ZITHROMAX® 500 mg azithromycin tablets.

JURISDICTION AND VENUE

6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*

7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '243 patent is invalid and not infringed.

8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.

9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

10. Teva USA holds Abbreviated New Drug Application ("ANDA") Number 65-153 for 250 mg azithromycin tablets; ANDA Number 65-150 for 600 mg azithromycin tablets and ANDA No. 65-193 for 500 mg azithromycin tablets.

11. On November 14, 2005, the United States Food and Drug Administration ("FDA") granted Teva USA approval to market 250 mg, 500 mg, and 600 mg azithromycin tablets pursuant to its ANDAs. Teva USA began marketing its 250 mg, 500 mg, and 600 mg azithromycin tablets on or about that date.

12. The active pharmaceutical ingredient ("API") in Teva USA's azithromycin tablets is azithromycin monohydrate hemiethanolate (the "hemiethanolate"). The hemiethanolate is a unique crystalline form of azithromycin, which has been patented by Teva Ltd.

13. Pfizer's '243 patent contains claims to azithromycin sesquihydrate (the "sesquihydrate"), which is a crystalline form of azithromycin different from the hemiethanolate.

14. Pfizer has demonstrated its intention to enforce the '243 patent against Teva USA and Teva Ltd. In particular, notwithstanding the fact that the API in Teva USA's azithromycin tablets is not the sesquihydrate, Pfizer has brought suit against Teva USA and Teva Ltd. in the District of Delaware claiming that Teva USA has been and is infringing the '243 patent by importing into the United States and selling and offering to sell within the United States its azithromycin tablets and that Teva Ltd. has actively induced Teva USA to infringe the '243 patent.

15. Pfizer has previously claimed that Teva USA's azithromycin tablets infringe one of its patents. In *Teva Pharmaceuticals USA, Inc. v. Pfizer, Inc.*, 03cv7423 and 04cv4979 (LAP) (consolidated), currently pending before this Court, Teva USA seeks a declaratory judgment that its azithromycin tablets do not infringe Pfizer's U.S. Patent No. 6,268,489 (the "'489 patent"), and that the '489 patent is invalid and unenforceable. The '489 patent claims "crystalline azithromycin dihydrate" ("dihydrate"), another crystalline form of azithromycin different from the hemiethanolate. Pfizer counterclaimed against Teva USA, alleging that Teva USA's sale of its azithromycin tablets would infringe the '489 patent.

16. Pfizer (or its predecessor) has also demonstrated its intention to protect other products from generic competition by Teva USA. On at least five occasions, Pfizer sued or maintained suit against Teva USA (or its related entities) for patent infringement relating to other drugs for which Teva USA has filed an ANDA: (i) *Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd.*, 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) *Pfizer Inc./Warner-Lambert v. Teva*, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) *Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.*, 01-cv-4995 (D.N.J.), concerning moexipril; (iv) *Bayer and Pfizer v. Biovail & Teva*, 01-cv-1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) *Warner-Lambert v. Teva USA*, 99-cv-0922 (D.N.J.), concerning quinipril.

17. Based on the above, an actual controversy exists between Teva USA, Teva Ltd. and Pfizer with respect to the '243 patent and Teva USA's 250 mg, 500 mg and 600 mg azithromycin tablets.

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

18. The allegations of Paragraphs 1 to 17 are incorporated by reference as if fully set forth herein.

19. Teva USA's manufacture, use, offer for sale, sale, and/or importation of its 250 mg, 500 mg and 600 mg azithromycin tablets pursuant to ANDA Nos. 65-153, 65-193 and 65-150, respectively, has not infringed and does not infringe any valid and properly construed claim of the '243 patent.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

20. The allegations of Paragraphs 1 to 19 are incorporated by reference as if fully set forth herein.

21. Teva Ltd. has not and is not actively inducing Teva USA to infringe any valid and properly construed claim of the '243 patent.

COUNT II
DECLARATORY JUDGMENT OF PATENT INVALIDITY

22. The allegations of Paragraphs 1 to 21 are incorporated by reference as if fully set forth herein.

23. The claims of the '243 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva USA and Teva Ltd. respectfully request the Court enter judgment against Pfizer to include:

A. A declaration that Teva USA's manufacture, use, importation, offer for sale or sale of Teva's azithromycin products pursuant to ANDA Nos. 65-153, 65-150, and 65-193 has not infringed and does not infringe any claim of United States Patent No. 6,977,243;

B. A declaration that Teva Ltd. has not directly or indirectly infringed, and is not directly or indirectly infringing, any claim of United States Patent No. 6,977,243;

C. A declaration that United States Patent No. 6,977,243 is invalid;

D. An award to Teva USA and Teva Ltd. of their reasonable costs and attorneys' fees in connection with this action;

E. An injunction prohibiting Pfizer and its officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, from threatening or charging infringement of, or instituting or maintaining any action for infringement of U.S. Pat. No. 6,977,243 against Teva USA or Teva Ltd., and

F. Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

KENYON & KENYON LLP

Dated: February 14, 2006 By: _____

Steven J. Lee (SL1043)
Elizabeth J. Holland (EH0850)
Sheila Mortazavi (SM3665)
Cynthia Lambert Hardman (CH2281)
One Broadway
New York, NY 10004
Tel.: (212) 425-7200

Fax: (212) 425-5288
Counsel for Plaintiffs, TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD. Plaintiffs, v. PFIZER INC Defendant.	Civil Action No. 06-CV-1134 (LAP)
PFIZER INC Counterclaim Plaintiff v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD. Counterclaim Defendants.	

PFIZER INC'S ANSWER AND COUNTERCLAIMS

Pfizer Inc ("Pfizer"), by and through its undersigned counsel, hereby files its Answer and Counterclaims in response to the Complaint For Declaratory Judgment ("Complaint") of Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (respectively "Teva USA" and "Teva Ltd."; collectively "Teva") in the above-captioned action in accordance with the numbered paragraphs in the Complaint. Except to the extent expressly and specifically admitted herein, such admissions being solely for the purpose of this action and none other, Pfizer denies each and every allegation

contained in the Complaint.

ANSWER

THE PARTIES

1. Admitted.

2. Admitted.

3. Admitted.

4. Admitted.

5. Admitted.

JURISDICTION AND VENUE

6. Pfizer admits that the Complaint purports to state a cause of action for a declaratory judgment allegedly based on claims arising under 35 U.S.C. §§ 1 *et seq.*, and thus this Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). All other allegations in paragraph 6 are denied on the basis that Pfizer lacks knowledge or information sufficient to form a belief as to their truth.

7. Denied.

8. Admitted.

9. Denied, as the proper venue for resolution of the issues raised by the Complaint is in the United States District Court for the District of Delaware, where Pfizer first filed its complaint charging Teva with infringing the '243 patent in suit.

THE PRESENCE OF AN ACTUAL CONTROVERSY

10. Admitted.

11. Admitted.

12. Denied.

13. Admitted.

14. Pfizer admits that on February 8, 2006, it filed a complaint against both Teva USA and Teva Ltd. for infringement of the '243 patent in the United States District Court for the District of Delaware before Teva USA and Teva Ltd. filed their complaint for declaratory judgment in this Court based on the '243 patent. All other allegations in paragraph 14 are denied.

15. Pfizer admits that the prior consolidated litigations captioned, *Teva Pharmaceuticals USA, Inc. v. Pfizer Inc*, 03cv7423 and 04cv4979 (LAP) (consolidated), that were before this Court, involved, *inter alia*, the '489 patent which is unrelated to the '243 patent; and that in the prior case Teva USA sought a declaratory judgment for, *inter alia*, alleged noninfringement, invalidity and unenforceability, and Pfizer counterclaimed alleging, *inter alia*, that Teva USA infringed the '489 patent. Pfizer denies that any issues of patent infringement remain pending before this Court in the prior consolidated cases, rather, the only remaining issue before this Court is Teva USA's proposed motion for attorney fees pursuant to 35 U.S.C. § 285. Pfizer admits that it owns the '489 patent and that the '489 patent claims are directed to crystalline azithromycin dehydrate, a crystalline azithromycin different from the hemiethanolate. All other allegations in paragraph 15 are denied.

16. Admitted.

17. Admitted that an actual controversy exists as alleged but all other allegations of this paragraph are denied.

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

18. Pfizer incorporates by reference and restates its answers to paragraphs 1-

17 as though fully set forth herein.

19. Denied.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

20. Pfizer incorporates by reference and restates its answers to paragraphs 1-19 as though fully set forth herein.

21. Denied.

COUNT III
DECLARATORY JUDGMENT OF PATENT INVALIDITY

22. Pfizer incorporates by reference and restates its answers to paragraphs 1-21 as though fully set forth herein.

23. Denied.

RESPONSE TO PRAYER FOR RELIEF

Pfizer denies that Teva is entitled to the relief sought in its "Prayer for Relief" in the Complaint.

COUNTERCLAIMS

Defendant and Counterclaim Plaintiff Pfizer hereby pleads the following Counterclaims against Teva USA and Teva Ltd., and requests relief as follows:

PARTIES

24. Pfizer incorporates by reference paragraphs 1, 2, 3, 4, 5, 10, and 11 of the Complaint and the above Answer, as if fully set forth herein.

25. Pfizer is a corporation organized and existing under the laws of the State of Delaware and has corporate offices at 235 East 42nd Street, New York, New York 10017.

26. Pfizer holds approved New Drug Application No. 050711 for azithromycin tablets for oral administration, 250 mg, which it sells under the registered name ZITHROMAX.

27. Pfizer holds approved New Drug Application No. 050784 for azithromycin tablets for oral administration, 500 mg, which it sells under the registered name ZITHROMAX.

28. Pfizer holds approved New Drug Application No. 050730 for azithromycin tablets for oral administration, 600 mg, which it sells under the registered name ZITHROMAX.

29. Pfizer also holds approved New Drug Application No. 050710 for azithromycin in an oral suspension (100 mg base/5ml and 200mg base/5 ml); approved New Drug Application No. 050693 for azithromycin in an oral suspension (1 gram base/packet); and approved New Drug Application No. 050733 for azithromycin in

injectable form (500 mg base/vial) -- all of which are sold by Pfizer under the registered name ZITHROMAX.

30. Counterclaim Defendant Teva USA is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454 and a manufacturing facility at 650 Cathill Road, Sellersville, Pennsylvania 18960.

31. Counterclaim Defendant Teva Ltd. is a corporation or other entity organized and existing under the laws of Israel, having its principal place of business at 5 Basel Street, Petach Tikva 49131, Israel. Teva USA is a wholly-owned subsidiary of Teva Ltd.

JURISDICTION AND VENUE

32. This Counterclaim for patent infringement arises under the patent laws of the United States, United States Code, Title 35. This Court has subject matter jurisdiction over this action pursuant to the provisions of United States Code, Title 28, §§ 1331 and 1338(a).

33. Personal jurisdiction exists over the Counterclaim Defendants Teva USA and Teva Ltd because they have come to this Court with their Complaint against Pfizer.

34. Denies that the United States District Court for the Southern District of New York is the proper venue to resolve this dispute.

THE PATENT-IN-SUIT

35. On December 20, 2005 the United States Patent and Trademark Office ("USPTO") issued the '243 patent, entitled "Crystal Forms of Azithromycin", based on

an application filed by Zheng J. Li and Andrew V. Trask and assigned to Pfizer. A true and complete copy of the '243 patent as issued is attached hereto as Exhibit A.

36. Errors appeared in the '243 patent as published on December 20, 2005, as a result of mistakes made by the USPTO.

37. On January 18, 2006, Pfizer filed a Request for Certificate of Correction to correct errors in the '243 patent.

38. On February 7, 2006, a Certificate of Correction of the '243 patent duly and legally issued and a true and complete copy of the Certificate of Correction is attached hereto as Exhibit B. The Certificate of Correction was published and appeared on the United States Patent and Trademark Office website on February 8, 2006.

39. The '243 patent, as corrected by the Certificate of Correction, covers azithromycin sesquihydrate.

40. Since its issue date, plaintiff Pfizer has been and remains the owner of all right, title and interest in and to the '243 patent, including its Certificate of Correction.

COUNTERCLAIM COUNT 1
(Patent Infringement)

41. The allegations of paragraphs 24-40 above are repeated and re-alleged as if set forth fully herein.

42. Upon information and belief, on or about November 14, 2005, Teva USA received approval for Abbreviated New Drug Application ("ANDA") No. 065153 for azithromycin tablets, 250 mg and continues to have such approval.

43. Upon information and belief, on or about November 14, 2005, Teva USA received approval for ANDA No. 065193 for azithromycin tablets, 500 mg and continues to have such approval.

44. Upon information and belief, on or about November 14, 2005, Teva USA received approval for ANDA No. 065150 for azithromycin tablets, 600 mg and continues to have such approval.

45. Upon information and belief, Teva USA began shipping azithromycin tablets, 250 mg, 500 mg and 600 mg, on, about or after November 14, 2005, and continues to do so.

46. Upon information and belief, the drug products containing azithromycin that were the subject of ANDA Nos. 065153, 065193 and 065150, contain azithromycin sesquihydrate and are covered by one or more claims of the '243 patent.

47. Upon information and belief, the azithromycin tablets, 250 mg, 500 mg and 600 mg, that Teva USA began shipping on, about or after November 14, 2005, contain azithromycin sesquihydrate and are covered by one or more claims of the '243 patent.

48. Upon information and belief Teva USA has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065153 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of tablets, 250 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

49. Upon information and belief Teva USA has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065193 seeking approval from the FDA to engage in the commercial manufacture, use, or sale of tablets, 500 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

50. Upon information and belief Teva USA has infringed the '243 patent under 35 U.S.C. § 271(e)(2)(A) by reason of ANDA No. 065150 seeking approval from

the FDA to engage in the commercial manufacture, use, or sale of tablets, 600 mg, containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

51. Upon information and belief Teva USA has infringed and continues to infringe one or more of the claims of the '243 patent under 35 U.S.C. § 271(a) by importing into the United States and offering to sell and selling within the United States a product containing azithromycin sesquihydrate prior to the expiration of the '243 patent.

52. Pfizer will be irreparably harmed if Teva USA is not enjoined from infringing the '243 patent.

COUNTERCLAIM COUNT II
(Active Inducement of Infringement)

53. Pfizer repeats and re-alleges paragraphs 24-52 above as if fully set forth herein.

54. On information and belief, defendant Teva Ltd. actively participated in the research and development of the azithromycin products which are the subject of ANDA Nos. 065153, 065193 and 065150 and was responsible for and controlled the preparation, filing and prosecution of these ANDAs.

55. On information and belief, defendant Teva Ltd. has actively engaged in activities relating to the importation, manufacture, use, sale or offer for sale of the azithromycin tablets, 250 mg, 500 mg and 600 mg that Teva USA began shipping on, about or after November 14, 2005, and those activities induced Teva USA to undertake such importation, manufacture, use, sale or offer for sale of the azithromycin tablets whereby Teva USA directly infringed one or more claims of the '243 patent.

56. Defendant Teva Ltd. is therefore liable as an infringer of the '243 patent under 35 U.S.C. § 271(b) by actively inducing defendant Teva USA to directly infringe the '243 patent.

57. Pfizer will be irreparably harmed if Teva Ltd. is not enjoined from inducing the infringement of the '243 patent.

COUNTERCLAIM COUNT III
(Declaratory Judgment of Infringement of the '243 Patent)

58. Pfizer repeats and re-alleges paragraphs 24-57 above as if fully set forth herein.

59. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties. Teva USA has taken immediate and active steps to continue the use, sale and/or offer for sale in the United States, of the azithromycin tablets, 250 mg, 500 mg and 600 mg that Teva USA began shipping on, about or after November 14, 2005.

60. Upon information and belief, Teva USA intends to offer to sell, sell or use within the United States, the azithromycin tablets, 250 mg, 500 mg and 600 mg that Teva USA began shipping on, about or after November 14, 2005, prior to the expiration of the '243 patent.

61. Upon information and belief, Teva USA's activities as described in paragraph 60 will infringe the '243 patent under 35 U.S.C. § 271(a).

62. Pfizer will be irreparably harmed if Teva USA is not enjoined from infringing the '243 patent.

COUNTERCLAIM COUNT IV
(Declaratory Judgment of Infringement of the '243 Patent)

63. Pfizer repeats and re-alleges paragraphs 24-62 above as if fully set forth herein.

64. This count arises under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, based upon an actual controversy between the parties. Teva Ltd. has taken immediate and active steps to actively induce Teva USA to continue the use, sale and/or offer for sale in the United States, of the azithromycin tablets, 250 mg, 500 mg and 600 mg that Teva USA began shipping on, about or after November 14, 2005.

65. Upon information and belief, Teva USA intends to offer to sell, sell or use within the United States, the azithromycin tablets, 250 mg, 500 mg and 600 mg that Teva USA began shipping on, about or after November 14, 2005, prior to the expiration of the '243 patent, and Teva Ltd. has actively induced Teva USA to engage in these activities.

66. Upon information and belief, Teva USA's activities as described in paragraph 65 will directly infringe the '243 patent under 35 U.S.C. § 271(a). Accordingly, Teva Ltd.'s activities as described in paragraph 65 will infringe the '243 patent under 35 U.S.C. § 271(b).

67. Pfizer will be irreparably harmed if Teva Ltd. is not enjoined from infringing the '243 patent.

PRAYER FOR RELIEF

WHEREFORE, Pfizer requests the following relief:

WITH RESPECT TO TEVA'S COMPLAINT

A. An order dismissing all counts of the Complaint with prejudice and denying all relief sought by Teva.

B. An order declaring that the '243 patent is valid, enforceable and has been

infringed by Teva.

WITH RESPECT TO PFIZER'S COUNTERCLAIMS

A. A judgment under 35 U.S.C. § 271 (a) that Teva USA's azithromycin product (250 mg tablet), which is marketed under approved ANDA No. 065153, infringes the '243 patent;

B. A judgment under 35 U.S.C. § 271 (a) that Teva USA's azithromycin product (500 mg tablet), which is marketed under approved ANDA No. 065193, infringes the '243 patent;

C. A judgment under 35 U.S.C. § 271(a) that Teva USA's azithromycin product (600 mg tablet), which is marketed under approved ANDA No. 065150, infringes the '243 patent;

D. A judgment under 35 U.S.C. § 271(e)(2)(A) that Teva USA infringed the '243 patent by submitting ANDA No. 065153 prior to the date of expiration of the '243 patent;

E. A judgment under 35 U.S.C. § 271(e)(2)(A) that Teva USA infringed the '243 patent by submitting ANDA No. 065193 prior to the date of expiration of the '243 patent;

F. A judgment under 35 U.S.C. § 271(e)(2)(A) that Teva USA infringed the '243 patent by submitting ANDA No. 065150 prior to the date of expiration of the '243 patent;

G. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065153 shall be a date not earlier than the date of expiration of the '243 patent;

H. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065193 shall be a date not earlier than the date of expiration of the '243 patent;

I. A judgment under 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of a product that is the subject of ANDA No. 065150 shall be a date not earlier than the date of expiration of the '243 patent;

J. A preliminary and permanent injunction enjoining Counterclaim Defendant Teva USA from making, using, selling, offering to sell, or importing a product containing azithromycin sesquihydrate until the date of the expiration of the '243 patent;

K. A judgment under 35 U.S.C. § 271 (b) that Counterclaim Defendant Teva Ltd. has actively induced defendant Teva USA to infringe the '243 patent;

L. A preliminary and permanent injunction enjoining Counterclaim Defendant Teva Ltd. from actively inducing infringement of the '243 patent;

M. A declaratory judgment that Teva USA's azithromycin product (250 mg tablet), which is marketed under approved ANDA No. 065153, will infringe the '243 patent;

N. A declaratory judgment that Teva USA's azithromycin product (500 mg tablet), which is marketed under approved ANDA No. 065193, will infringe the '243 patent;

O. A declaratory judgment that Teva USA's azithromycin product (600 mg tablet), which is marketed under approved ANDA No. 065150, will infringe the '243 patent;

P. A declaratory judgment that Counterclaim Defendant Teva Ltd. will

actively induce defendant Teva USA to infringe the '243 patent;

Q. An award of damages to Pfizer as a result of Teva's infringement of the '243 patent, altogether with interest and costs pursuant to 35 U.S.C. § 271(e)(4)(C);

R. An award of damages to Pfizer as a result of Teva's infringement of the '243 patent, altogether with interest and costs pursuant to 35 U.S.C. § 284;

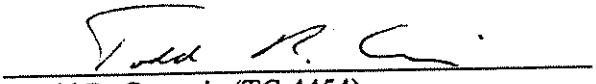
S. A declaration by this Court that this an exceptional case and an order that Teva pay to Pfizer its reasonable attorneys' fees, costs and interest in this action, pursuant to 35 U.S.C. § 285; and

T. Such further and other relief as this Court may deem just and proper.

Dated: March 7, 2006
New York, New York

Respectfully submitted,

JONES DAY

By: 

Todd R. Geremia (TG 4454)
222 East 41st Street
New York, New York 10017
(212) 326-3939 (telephone)
(212) 755-7206 (facsimile)

Attorneys for Defendant / Counterclaim Plaintiff, Pfizer Inc.

Of Counsel
Rudolf E. Hutz
William E. McShane
Daniel C. Mulveny
Connolly Bove Lodge & Hutz LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899-2207
(302) 658-9141 (telephone)
(302) 658-5614 (telefax)

CERTIFICATE OF SERVICE

I certify that I caused a true and correct copy of the foregoing Pfizer Inc.'s Answer and Counterclaims to be served upon the following counsel for the plaintiff in this action by overnight mail on March 7, 2006:

Elizabeth J. Holland, Esq.
KENYON & KENYON LLP
One Broadway
New York, NY 10004

Attorney for Plaintiffs / Counterclaim Defendants, Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd.

Dated: March 7, 2006
New York, New York

Todd R. Geremia

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EXHIBIT E

US006268489B1

(12) **United States Patent**
Allen et al.

(10) **Patent No.: US 6,268,489 B1**
(45) **Date of Patent: Jul. 31, 2001**

(54) **AZITHROMYCIN DIHYDRATE**

(75) Inventors: **Douglas J. M. Allen**, New London; **Kevin M. Nepveux**, Old Saybrook, both of CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **07/994,040**

(22) Filed: **Dec. 21, 1992**

Related U.S. Application Data

(63) Continuation of application No. 07/449,961, filed on Dec. 11, 1989, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 9, 1987 (WO) PCT/US87/01612

(51) **Int. Cl.**[7] **C07H 17/08**
(52) **U.S. Cl.** **536/7.4**; 536/18.5
(58) **Field of Search** 536/7.4, 18.5

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,020,270		4/1977	Arcamone et al.	536/18
4,219,641	*	8/1980	Deposato et al.	536/7.2
4,474,768	*	10/1984	Bright	514/29
4,512,982	*	4/1985	Hauske et al.	536/7.2
4,517,359		5/1985	Kobrehel et al.	536/7.4
4,526,889		7/1985	Bright	514/29
4,963,531		10/1990	Remington	514/29

OTHER PUBLICATIONS

Pelizza et al., Farmaco–Ed.Sc., 31, 254–262 (1976).
Allen et al., J. Pharm. Sci., 67, 1087–1093 (1978).

* cited by examiner

Primary Examiner—Elli Peselev
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; Mervin E. Brokke

(57) **ABSTRACT**

Non-hygroscopic, azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) dihydrate and a process therefor.

3 Claims, No Drawings

AZITHROMYCIN DIHYDRATE

This is a continuation of application Ser. No. 07/449,961, filed on Dec. 11, 1989 now abandoned as a request for U.S. examination of International Application No. PCT/US87/01612, filed Jul. 9, 1987.

BACKGROUND OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A), viz., a non-hygroscopic dihydrate form thereof.

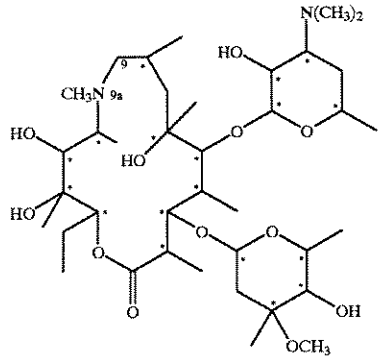
Azithromycin is the U.S.A.N. (generic name) for 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, a broad spectrum antibacterial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. The name "N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A" was employed in these patents. The present more systematic name is based upon the ring expansion and replacement nomenclature of the "IUPAC Nomenclature of Organic Chemistry, 1979 Edition," Pergamon Press, 1979, pp. 68–70, 459, 500–503.

As previously crystallized from ethanol and water (e.g., Example 3 of U.S. Pat. No. 4,474,768), azithromycin was obtained as a hygroscopic monohydrate (for details, see Preparation 1 below). Because of its hygroscopic nature, it is most difficult to prepare and maintain this prior monohydrate product in a form having a constant, reproducible water-content. It is particularly difficult to handle during formulation, since at higher relative humidity levels which are generally required to avoid electrostatic problems (e.g., flow rates, dusting with potential for explosion), the monohydrate readily picks up varying amounts of water, the amount depending upon exposure time and the precise value of the relative humidity (see Preparation 1 below). Such problems have been overcome by the present invention of a stable dihydrate which is essentially non-hygroscopic under conditions of relative humidity conducive to formulation of azithromycin.

SUMMARY OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin, viz., a crystalline, non-hygroscopic dihydrate, prepared by crystallization from tetrahydrofuran and an aliphatic (C_5–C_7)hydrocarbon in the presence of at least two molar equivalents of water.

Azithromycin is of the formula



It is derived from erythromycin A without involvement of asymmetric centers, and so has stereochemistry at each of these centers (*) which is identical with that of erythromycin A. Named systematically as an erythromycin A derivative, the compound is called 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A. Azithromycin, including the present dihydrate, possess broad-spectrum antibacterial activity useful in the treatment of susceptible bacterial infections in mammals, including man.

The expression "aliphatic (C_5–C_7)hydrocarbon" refers to lower boiling hydrocarbon solvents, frequently mixtures of particular boiling point ranges such as those generally referred to as "pentane", "hexane", "hexanes", etc., but which may also be substantially pure, e.g., n-hexane, cyclohexane or methylcyclohexane. A preferred hydrocarbon solvent is so-called "hexane", having a boiling point which ranges near that of pure n-hexane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is readily carried out. Azithromycin, prepared according to Bright or Kobrehel et al. (cited above) in amorphous form, or as the monohydrate (which may contain, because of its hygroscopicity, more than one molar equivalent of water) is dissolved in tetrahydrofuran. Since the temperatures required for the initial stages of the present process are not critical, ambient temperatures are generally employed, avoiding the cost of heating and cooling. Furthermore, to maximize yield and minimize solvent, labor and equipment costs, the volume of tetrahydrofuran is kept to a near minimum, e.g., 2 liters of solvent per kilogram of substrate. Any insoluble impurities which may be present at this stage are readily removed by conventional methods of filtration. If necessary, the mixture can be decolorized with activated carbon. If desired, the highly concentrated mixture can be diluted with a portion of (C_5–C_7)hydrocarbon prior to filtration, in order to facilitate handling. If the water content of the ingoing bulk is much greater than one molar equivalent, e.g., approaching 2-molar equivalents, it is preferable to dry the mixture for a short period of time over a drying agent such as $MgSO_4$, particularly if hydrocarbon solvent is to be added prior to filtration. To obtain the crystalline dihydrate, water is added to the resulting clear solution, in an amount sufficient to bring the total water content to a level corresponding to at least two molar equivalents, generally not exceeding a level of about 3–4 molar equivalents. The level of water present in the

system is readily monitored by standard Karl Fischer titration. The addition of water is followed by the addition of the hydrocarbon solvent (or of more hydrocarbon solvent, if the mixture was previously diluted before filtration), leading to crystallization of the desired dihydrate product. This stage of the process can be carried out at ambient temperature (e.g. 17–30° C.), but to facilitate the initial crystallization, is preferably carried at slightly elevated temperature (e.g. 30–40° C.). The total volume of hydrocarbon solvent employed is generally at least about four times in volume that of the tetrahydrofuran. Higher volumes of hydrocarbon are satisfactory, but are generally avoided in the interest of minimizing cost. Once crystallization is complete, the product is recovered by filtration, usually after a period of granulation (e.g., 3–24 hours) at ambient temperature. The product is usually vacuum dried of organic solvents (at 20–40° C., conveniently at ambient temperature). To avoid loss of water of hydration, the volatiles and water-content are generally monitored during drying, such that the level of tetrahydrofuran and hydrocarbon will generally fall below 0.25% and the water content will be within 0.3% of theory (4.6%).

Azithromycin dihydrate is formulated and administered in the treatment of susceptible bacterial infections in man according to methods and in amounts previously detailed by Bright, U.S. Pat. No. 4,474,768, cited above and hereby incorporated by reference.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Non-Hygroscopic Azithromycin Dihydrate

Method A

The hygroscopic monohydrate of Preparation 1 (100 g; water-content:3.1%), tetrahydrofuran (220 ml) and diatomaceous earth (5 g) were combined in a 500 ml Erlenmyer flask, stirred for 30 minutes and filtered with 20 ml of tetrahydrofuran wash. The combined filtrate and wash was transferred to a 3 liter round bottom flask. The solution was stirred vigorously and H_2O (2.0 ml) was added. After 5 minutes, hexane (1800 ml) was added over 5 minutes, with continued vigorous stirring. Following an 18 hour granulation period, title product was recovered by filtration with 1×10 ml hexane wash, and dried in vacuo to 4.6±0.2% H_2O by Karl Fischer, 89.5 g.

Method B

The hygroscopic monohydrate of Preparation 1 (197.6 g) and tetrahydrofuran (430 ml) were charged to a reactor and the mixture stirred to achieve a milky white solution. Activated carbon (10 g) and diatomaceous earth (10 g) were added and the mixture stirred for 15 minutes, then diluted with 800 ml of hexane and filtered with suction over a pad of diatomaceous earth with 250 ml of hexane for wash. The combined filtrate and wash was diluted to 2500 ml with hexane and warmed to 34° C. With stirring, 24.7 ml of H_2O was added. The mixture was allowed to cool to room temperature, granulated for five hours and title product recovered and dried as in Method A, 177.8 g.

The dihydrate melts sharply at 126° C. (hot stage, 10°/minute); differential scanning calorimetry (heating rate, 20° C./minute) shows an endotherm at 127° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 1.8% weight loss at 100° C. and a 4.3% weight loss at 150° C.; ir (KBr) 3953, 3553, 3488, 2968, 2930, 2888, 2872, 2827, 2780, 2089, 1722, 1664, 1468, 1426, 1380, 1359, 1344, 1326, 1318, 1282, 1270, 1252, 1187, 1167, 1157, 1123, 1107, 1082, 1050, 1004, 993, 977, 955, 930, 902, 986, 879, 864, 833, 803, 794, 775, 756, 729, 694, 671, 661, 637, 598, 571, 526, 495, 459, 399, 374, 321 and 207 cm^{-1}; $[alpha]^{26}_{D}$=41.4° (c=1, $CHCl_3$).

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}.2H_2O$: C, 58.14; H, 9.77; N, 3.57; OCH_3, 3.95; H_2O, 4.59. Found: C, 58.62; H, 9.66; N, 3.56; OCH_3, 4.11; H_2O, 4.49. Neutralization Equivalent (0.5N HCl in 1:1 CH_3CN:H_2O): Calcd.: 374.5. Found: 393.4.

Samples of a dihydrate, slightly over dried to contain 4.1% water (less than theoretical) rapidly picked-up water at 33%, 75% or 100% relative humidities to achieve the theoretical water content (4.6%) for the dihydrate. At 33% and 75% relative humidities, water content remained essentially constant for at least 4 days. At 100% relative humidity, the water content further rose to about 5.2, where it remained essentially constant of the next three days.

A sample of the same dihyrate, maintained at 18% relative humidity gradually lost water. At four days, the water content was 2.5% and at 12 days, 1.1%.

PREPARATION 1

Hygroscopic Azithromycin Monohydrate

Substantially following the methylation procedure of Kobrehel et al., U.S. Pat. No. 4,517,359; and the crystallization procedure of Bright, U.S. Pat. No. 4,474,768; 9-deoxo-9a-aza-9a-homoerythromycin A (previously called 11-aza-10-deoxo-10-dihydroerythromycin A; 100 g, 0.218 mol) was dissolved with stirring in 400 ml $CHCl_3$. Formic acid (98%; 10.4 ml, 0.436 mol) and formaldehyde (37%; 16.4 ml, 0.349 mol) were added over 4–5 minutes, and the mixture heated at reflux for 20 hours. The mixture was cooled to ambient temperature, diluted with 400 ml H_2O and adjusted to pH 10.5 with 50% NaOH. The aqueous layer was separated and extracted 2×100 ml with fresh $CHCl_3$. The organic layers were combined, stripped in vacuo to 350 ml, twice diluted with 450 ml of ethanol and restripped to 350 ml, and finally diluted with 1000 ml H_2O over a 1 hour period, pausing for 15 minutes as a slurry began to develop after the addition of about 250 ml of H_2O. Title product was recovered by filtration and dried in air at 50° C. for 24 hours, 85 g; mp 136° C.; differential thermal analysis (heating rate 20° C./minute) shows an endotherm at 142° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 2.6% weight loss at 100° C. and a 4.5% weight loss at 150° C.; water content 3.92%; ethanol content 1.09%.

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}$ (corrected for ethanol and water content): C, 58.46; H, 9.78; N, 3.74; Alkoxy, 4.67. Found: C, 58.40; H, 9.29; N, 3.50; Alkoxy, 4.52.

A sample of the monohydrate (having a water content of 3.2%) was maintained at 18% relative humidity for 14 days. The sample lost water over the first 24 hours to yield monohydrate having the theoretical water content (2.35%). The water content then remained substantially constant over 14 days, a value of 2.26% being recorded at 14 days.

At 33% relative humidity the water content of a sample of the same monohydrate rapidly rose to 5.6% where it remained substantially steady for at least three days. Similarly at 75% and 100% relative humidity, the water content rose rapidly, but was now maintained at even higher levels, 6.6% and 7.2%, respectively, for at least 3 days.

What is claimed is:

1. Crystalline azithromycin dihydrate.

2. A method of preparing crystalline azithromycin dihydrate which comprises crystallization of amorphous azithromycin or azithromycin monohydrate from a mixture of tetrahydrofuran and a (C_5–C_7) aliphatic hydrocarbon in the presence of at least 2 molar equivalents of water.

3. A method of claim 2 wherein the hydrocarbon is hexane.

* * * * *

EXHIBIT F

US005605889A

United States Patent [19]

Curatolo et al.

[11] **Patent Number: 5,605,889**

[45] **Date of Patent: Feb. 25, 1997**

[54] **METHOD OF ADMINISTERING AZITHROMYCIN**

[75] Inventors: **William J. Curatolo**, Niantic; **George H. Foulds**, Waterford, both of Conn.; **Hylar L. Friedman**, Brattleboro, Vt.

[73] Assignee: **Pfizer Inc.**, New York, N.Y.

[21] Appl. No.: **235,069**

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[51] **Int. Cl.**[6] **A61K 31/70**; A61K 9/14; A61K 9/20

[52] **U.S. Cl.** **514/29**; 514/960; 424/464; 424/465; 424/474; 424/480; 424/481; 536/7.2

[58] **Field of Search** 514/29, 960; 536/7.2; 424/464, 465, 474, 480, 481

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Zithromax (Trademark of Pfizer, Inc.) Capsules Package Insert for azithromycin capsule dosage form sold commercially in U.S.

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; James T. Jones

[57] **ABSTRACT**

An oral dosage form of azithromycin which does not exhibit an adverse food effect; Specific azithromycin oral dosage forms including tablets, powders for oral suspensions and unit dose packets; Methods of treating microbial infections with the dosage forms; And therapeutic packages containing the dosage forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZITHROMYCIN

This invention relates to a dosage form of azithromycin, and also to a method of treating a microbial infection which involves administering azithromycin in the fed state to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.

In general, it is known that the absorption and bioavailability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gastrointestinal (GI) tract because, in general, the gastric residence time of a drug is usually significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important inasmuch as, when a drug exhibits an adverse food effect, there is risk associated with administering it to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug bioavailability, the following being a non-comprehensive listing:

(1) The particular dosage form can affect bioavailability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may vary depending on whether the subject has eaten or is fasted.

(2) The pH of the stomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected accordingly.

(3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal eaten. For example some vegetables (such as brussels sprouts) can stimulate first pass metabolism of some drugs, but not others. Grapefruit juice, on the other hand, may inhibit first pass metabolism of some drugs.

(4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to solubilize poorly soluble drugs and thus increase bioavailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional factors include, for example, pH-dependent solubility, site-specific intestinal permeation rate, instability to intestinal enzymes, susceptibility to first pass metabolism, and instability to colonic bacteria. Given the plethora of factors which can influence bioavailability, there usually is no way to predict, in the absence of actual testing, whether a particular drug will exhibit a food effect. For example, Toothaker and

Welling, *Ann. Rev. Pharmacol. Toxicol.*, 1980, 173–99, discuss various drugs whose absorption is delayed in the presence of food (cephalexin, cefaclor, metronidazole, aspirin, alclofenac, indoprofen, digoxin, cimetidine), whose absorption may be unaffected by food (ampicillin, erythromycin estolate, spiramycin, propylthiouracil, oxazepam, bendroflumethiazide), and whose absorption is increased in the presence of food (erythromycin ethylsuccinate, nitrofurantoin, 8-methoxsalen, propranolol, metoprolol, dicoumarol, diazepam, hydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Toothaker and Welling review studies which demonstrate food related reduced absorption for tablet dosage forms of erythromycin stearate, aspirin, nafcillin, and sotalol.

In the case of azithromycin, at least one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state, and it has heretofore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at least one hour before or two hours following a meal.

It would accordingly be useful if azithromycin could be administered to patients that have eaten recently and also if a dosage form for azithromycin were available which could be administered to patients that have eaten, as well as patients in a fasted state.

SUMMARY OF THE INVENTION

This invention provides an oral dosage form of azithromycin which can be administered to a mammal (including humans) that has eaten and which exhibits substantially no adverse food effect, excluding any dosage form which contains a significant amount of an alkaline earth oxide or hydroxide. The dosage form exhibits a mean $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "$(AUC_{fed})/(AUC_{fst})$" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithromycin dosage form which does not exhibit an adverse food effect. The dosage form comprises azithromycin and a pharmaceutically acceptable carrier, as hereinafter further detailed and described. The dosage form is in the form of a tablet (including both swallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a suspension made from a unit dose packet, in the form of a powder for oral suspension, and in the form of an oral suspension per se. It is noted that when a unit dose packet is constituted, it is probably mainly in the form of a suspension if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "suspension" herein is intended to embrace liquids containing azithromycin partially in suspension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits substantially no adverse food effect. The dosage form employed exhibits a

mean $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "eaten" means that the mammal has eaten food of any sort within one hour prior to dosing up to two hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra of the term "dosage form" for purposes of this invention.

Capsules as a dosage form do not form a part of the invention.

For purposes of this invention azithromycin may be administered alone or in combination with other therapeutic agents.

A food effect can be detected and quantified as described, for example in Toothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in μg/mL) of azithromycin along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient test population and are, therefore, mean values averaged over the entire test population. By measuring the area under the curve for a fed population of subjects (AUC_{fed}) and comparing it with the area for the same population of fasted subjects (AUC_{fst}), it can be determined whether a given drug exhibits an adverse food effect or not.

For definitional purposes of this invention, and specifically with respect to azithromycin dosage forms only, a dosage form of azithromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean $(AUC_{fed})/(AUC_{fst})$ is below the value 0.80 and/or the lower 90% confidence limit for this ratio is below 0.75.

Conversely, a dosage form of azithromycin which does not exhibit an adverse food effect is one which, when tested on a test population, exhibits a value for $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 and a lower 90% confidence limit for this value of at least 0.75. The value for mean $(AUC_{fed})/(AUC_{fst})$ can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of 1.40 or below.

A population of "fed" subjects, for purposes of definition and for measuring AUC_{fed}, is one made up of subjects each of whom has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., swallowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be consumed within the twenty minute period and the subject still qualifies as "fed". A "fasted subject" for purposes of definition and for measuring AUC_{fst} is one who has not eaten for at least eight hours, typically overnight, prior to ingestion of the dosage form.

The 90% confidence limits on AUC_{fed}/AUC_{fst} for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schuirman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was carried out using Statistical Analysis System (SAS) software from SAS Institute, Cary, N.C. SAS procedure referred to in the SAS software as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fed/Fasted) effects. The sequence effect was tested using the [subject within sequence] mean square from the analysis of variance (ANOVA) as an error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least square means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these estimates, as the difference plus (or minus) the standard error of the difference times the 95th percentile of the t-distribution with (twice the sample size-2) degrees of freedom. The anti-log was taken on the limits to obtain the corresponding confidence for the ratio.

That a dosage form according to the invention does not exhibit an adverse food effect is surprising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stomach acid. The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus, without being bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly assigned co-pending application Ser. No. 07/922,262 filed Jul. 30, 1992 discloses taste masking compositions of bitter pharmaceutical agents, such as azalide antibiotics, containing, as a taste-masking component, a basic compound selected from the group consisting of alkaline earth oxides and alkaline earth hydroxides. A composition of this invention, if it contains an alkaline earth oxide or hydroxide at all, contains less than a taste-masking amount of the taste-masking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth oxide or hydroxide, and may be free of such taste-masking component entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside these limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and also anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2.

In order to test whether a particular azithromycin dosage form exhibits an adverse food effect, the most reliable method is actually to test the dosage form in vivo on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithro-

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio $(AUC_{fed})/(AUC_{fst})$ exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds 0.75.

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution in the GI tract, or at least provides azithromycin for dissolution within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least about 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule dosage form comprising azithromycin is also considered to fall within the scope of the appended claims if it satisfies the in vitro dissolution testing requirements enumerated herein. An azithromycin dosage form according to the invention exhibits at least about 90% dissolution of azithromycin within about 30 minutes, preferably within 15 minutes, when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37° C. with paddles turning at 100 rpm. This test is described in US Pharmacopaca XXII, pp. 1578–1579. Dosage forms which pass this test under more stringent conditions (lower volume of buffer, greater amount of dosage form, lower temperature, higher pH, lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azithromycin dosage form in this in vitro test is believed to be an indicator of the time required for dissolution of the dosage form in the GI environment. The following discussion is believed pertinent in this regard.

It is generally assumed and observed that the in vitro dissolution rate of dosage forms exhibits a rank order correlation with in vivo dissolution, particularly for a single dosage form type, e.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves an important role in control of the quality of manufactured dosage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the artificial conditions of an in vitro dissolution test (e.g. vessel geometry, stirring rate, stirring method, and so forth) are not identical to the conditions under which a dosage form disintegrates and dissolves in the GI tract.

When comparing dosage forms of different type, e.g. capsules and tablets, in vitro dissolution rate should correlate roughly with in vivo dissolution rate. However, subtle differences exist between the disintegration mechanisms of capsules and tablets. For capsules, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dissolve first at the capsule ends, and later at the capsule center. Tablets, on the other hand, disintegrate homogeneously. Thus subtle differences may exist in the in vitro/in vivo dissolution correlation when comparing capsules and tablets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may exhibit subtle differences in in vivo dissolution rate. While such subtle differences may have no therapeutically significant effect on systemic bioavailability of an orally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-containing capsules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally dosed. In fact, this has been observed for azithromycin, as exemplified in the Examples herein.

For the in vitro dissolution studies disclosed herein, azithromycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chromatographic column (15 cm×0.4 cm), and a 5 micron alumina based hydrocarbonaceous spherical particle precolumn (5 cm×0.4 cm) (both available from ES Industries, Marlton, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonitrile (pH 11) was used, with electrochemical detection (e.g. Bioanalytical Systems, West Lafayette, Ind., LC-4B amperometric detector with dual series glassy carbon electrodes).

For in vivo food effect studies, serum azithromycin is assayed using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog. Biomed. Appl. 565, 321–337, with amperometric electochemical detection. Alternatively, any assay method that produces equivalent results, for example, bioassay, can be used.

Tablets according to the invention contain, as necessary ingredients, azithromycin and a disintegrant. Examples of tablet disintegrants are starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (sodium croscarmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), clays (e.g. magnesium aluminum silicate), microcrystalline cellulose (of the type available under the registered trademark Avicel from FMC Corp. or the registered trademark Emcocel from Mendell Corp., Carmel, N.Y.), alginates, gums, surfactants, effervescent mixtures, hydrous aluminum silicate, cross-linked polyvinylpyrrolidone (available commercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Preferred disintegrants for azithromycin tablets are sodium croscarmellose (Ac-Di-Sol), sodium starch glycolate (available commercially under the registered trademarks Primojel from Avebe (Union, N.J.) or Generichem, (Little Falls, N.J.) and Explotab from Mendell Corp.), microcrystalline cellulose (Avicel), and cross-linked polyvinylpyrrolidone (PVP-XL). Azithromycin tablets of this invention comprise azithromycin and 1–25% disintegrant, preferably 3–15% disintegrant based on total tablet weight. For example, a 463.5 mg tablet (250 mg activity azithromycin) may contain 9 mg sodium croscarmellose and 27 mg pregelatinized starch.

In addition to the active ingredient azithromycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the exact formulation, such as binders, flavorings, buffers, diluents, colors, lubricants, sweetening agents, thickening agents, and glidants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Examples of binders are acacia, cellulose derivatives (such as methylcellulose and carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose), gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, starch paste, sucrose, sorbitol, pregelatinized starch, gum tragacanth,

alginic acids and salts thereof such as sodium alginate, magnesium aluminum silicate, polyethylene glycol, guar gum, bentonites, and the like. A preferred binder for azithromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Point, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth. The amount of flavoring may depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by weight based on the total tablet weight, when a flavor is used.

A variety of materials may be used as fillers or diluents. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. starch 1500), cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emcompress from Mendell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Monmouth Junction, N.J.), calcium carbonate, calcium sulfate, and others as known in the art.

Lubricants can also be employed herein in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants are magnesium stearate, stearic acid, glycerylbehaptate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art. Preferred lubricants are magnesium stearate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise 0.5 to 7.0% of the total tablet weight.

Other excipients such as glidants and coloring agents may also be added to azithromycin tablets. Coloring agents may include titanium dioxide and/or dyes suitable for food such as those known as F. D. & C, dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be added extragranularly. Alternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tablets may also be coated, with a coating that exhibits little or no effect on or interference with tablet dissolution, to assure ease of swallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are film-coated to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropylmethylcellulose (HPMC). HPMC may be obtained commercially, for example from Colorcon Corp., in coating formulations containing excipients which serve as coating aids, under the registered trademark Opadry. Opadry formulations may contain lactose, polydextrose, triacetin, polyethyleneglycol, polysorbate 80, titanium dioxide, and one or more dyes or lakes. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press. Tablet formulation and conventional processing techniques have been widely described, for Example in *Pharmaceutical Dosage Forms: Tablets;* Edited By Lieberman, Lachman, and Schwartz; Published by Marcel Dekker, Inc., 2d Edition, Copyright 1989, the text of which is herein incorporated by reference.

The azithromycin dosage forms of this invention also include powders to make oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-caking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmacist. The oral suspension is thus the actual dosage form ingested by patients. The typical shelf life for a suspension is about five days because azithromycin therapy is generally of five days duration.

Azithromycin suspensions according to the invention contain, as necessary ingredients in addition to azithromycin, one or more thickening agents in a total amount of 0.1 to 2%, and a buffer or pH-altering agent in an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used in an amount from 0.1 to 2%.

Suitable thickening agents function as suspending agents and include, for example, hydrocolloid gums known for such purpose, examples of which include xanthan gum, guar gum, locust bean gum, gum tragacanth, and the like. Alternatively, synthetic suspending agents may be used such as sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like.

Dispersing agents include colloidal silicon dioxide, available from Cabot Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masked by including a basic buffer or pH-altering agent which will provide a pH of approximately 10 in the constituted suspension. Maintenance of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masks the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mask the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, artificial creme de vanilla #11489, and spray-dried artificial banana #15223 available commercially from Bush Boake Allen, Inc., Chicago, Ill. Artificial sweeteners may also be used.

A powder used to make a suspension herein may also contain conventional optional ingredients such as (1) wetting agents such as sorbitan monolaurate, polysorbate 80, and sodium lauryl sulfate; (2) anti-foaming agents and (3) sweeteners and fillers such as glucose. The powder may also contain a buffer to maintain a high pH upon reconstitution, as discussed above. Suitable buffers and pH-altering agents

include anhydrous tribasic sodium phosphate, anhydrous sodium carbonate, glycine, and the like. Suitable preservatives are well known, for example sodium benzoate and the like. After swallowing, azithromycin from a suspension dissolves quickly.

In the preparation of azithromycin powder for oral suspension formulations, all ingredients may be blended together and deagglomerated, as known in the art. Preferably, azithromycin and flavors are blended, and other ingredients are separately blended. Finally, these two blends are blended and deagglomerated.

Preferred oral suspensions are those which resuspend easily after constitution with aqueous media and which do not cake on storage after constitution. Preferred suspensions contain sucrose NF, when sucrose is used, and anhydrous excipients when available, to assure facile suspension upon constitution. The drug-containing powder is generally reconstituted with water.

Suspensions of this invention exhibit about 90% dissolution of azithromycin in vitro in about 15 minutes. The test can be summarized as follows:

Shake the azithromycin-containing bottle to loosen the powder, and constitute the sample as per label instructions, e.g. as described in Example 12 to provide a 40 mg/ml azithromycin suspension. Shake the bottle vigorously for 2 minutes, then allow the bottle to sit for 30 minutes. Shake again vigorously for 15 seconds. Withdraw 5 ml from the bottle (typically equivalent to 200 mg of azithromycin), taking care to eliminate air bubbles. Carefully dispense the 5 ml aliquot of the azithromycin suspension approximately 10 cm over the surface of the dissolution medium (0.10M sodium phosphate buffer, pH 6.0) in a USP Apparatus 2, with the paddles positioned 2.5 cm from the bottom of the vessels. Begin rotating the paddles at 25 rpm, after the Oral Suspension samples have sunk to the bottom of the vessels. Remove approximately 10 ml from the dissolution vessel at each sampling time, filter, and assay filtrate for azithromycin using the HPLC assay described previously.

An azithromycin unit dose packet dosage form (also referred to herein as a "sachet") consists of a unit packet, designed to be emptied into an aqueous vehicle, for example water or a natural or artificial fruit beverage. The packet contains a blend of azithromycin and excipients which is thus reconstituted. The packet contains, as necessary ingredients, azithromycin and a dispersing agent which makes the sachet powder free flowing, for example colloidal silicon dioxide such as Cab-O-Sil from Cabot. Generally the dispersing agent is present in an amount of about 0.2 to 2.0% by weight based on the weight of the dry sachet as it is to be sold. The dispersing agent also serves as a glidant. The formulation may also optionally contain ingredients including (1) a filler or sweetener (e.g. glucose); (2) a buffer (e.g. sodium phosphate); (3) a wetting agent such as a surfactant, for example sodium lauryl sulfate, and (4) flavors such as any of those enumerated herein, and the like. The powder in the packet flows freely and disperses quickly, essentially immediately upon stirring when reconstituted. Azithromycin unit dose packet dosage forms may be prepared by blending and deagglomerating all ingredients, as known in the art. Preferably, the filler (e.g. sucrose), buffer (e.g. anhydrous tribasic sodium phosphate), and glidant (e.g. colloidal silicon dioxide) are blended and deagglomerated, followed by blending with azithromycin and flavors, followed by deagglomeration. The azithromycin in the packet dissolves quickly when evaluated as follows. The contents of a packet are added to a 250 ml beaker containing 60 ml water treated with the Milli-Q Plus system, Millipore Corp. (>18 megohms resistivity). The contents of the beaker are stirred with a spoon until a homogeneous suspension is obtained (1–2 min.). With the paddles raised, the suspension is poured into the center of a dissolution vessel of a USP-2 dissolution apparatus containing 900 ml 0.1M sodium phosphate buffer, pH 6.0. The paddles are then lowered into the vessel, and rotation is begun at 50 rpm. 10 mL aliquots are removed at each time point, filtered, and filtrates are assayed for azithromycin in solution, using an HPLC assay as described above. Using this method, greater than 90% dissolution of a 1 gm azithromycin packet is observed in less than 5 minutes. The packet thus does not exhibit an adverse food effect.

As stated, the oral azithromycin dosage forms disclosed and described above can be administered to a mammal, including man, in need of such treatment when the mammal has eaten, regardless of how recently and of the nature and quantity of food, without exhibiting an adverse food effect. To this end, and as an additional feature of the invention, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said package, written (i.e., printed) matter non-limited as to whether the dosage form can be taken with or without food. The written matter is of the type containing information and/or instructions for the physician, pharmacist or patient. The written material can be "non-limited as to whether the dosage form can be taken with or without food" by virtue of including no statement regarding whether or not the dosage form can be taken with or without food, i.e. the statement is silent with regard to food effects. Alternatively, the written material can be non-limited by containing one or more statements affirmatively informing the user (i.e., the patient, pharmacist, or physician) that the said oral dosage form can be taken by or administered to a patient regardless of whether the patient has eaten or otherwise imbibed food (optionally, for example, also stating something like "without regard to type or quantity of food"). The written material can not contain limiting language with respect to food, e.g, "This dosage form can not be taken with food" or "This dosage form may only be given after the patient has fasted" or the like.

The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual dosages for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Printed or otherwise written matter is associated with the package in which the azithromycin dosage form is sold. The term "associated with" is intended to include all manners in which written matter, such as instructional or informational materials can be associated with a medicament, as known conventionally in the art. Thus written matter can be associated with the container, for example, by being: written on a label (e.g., the prescription label or a separate label) adhesively affixed to a bottle containing an azithromycin suspension; included inside a container as a written package insert, such as inside a box which contains unit dose packets; applied directly to the container such as being printed on the wall of a box; or attached as by being tied or taped, for example as an instructional card affixed to the neck of a bottle via a string, cord or other line, lanyard or tether type device. The written matter may be printed directly on a unit dose pack or blister pack or blister card. If the written matter affirmatively contains a non-limiting statement, the written

matter may contain other information in addition. An affirmative non-limiting statement may, for example, read like the following exemplary statement:

> This product does not exhibit an adverse food effect and may accordingly be administered to patients whether or not they have eaten and without regard to type or quantity of food.

or something similar, such as "may be taken without regard to food".

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate that (1) azithromycin capsules exhibit an adverse food effect, and that more slowly dissolving capsules exhibit a larger food effect, and (2) azithromycin fast dissolving tablet, powder for oral suspension, and unit dose packet dosage forms do not exhibit an adverse food effect.

EXAMPLE 1

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form with moderate dissolution rate.

Capsules were prepared which contained 250 mg activity azithromycin. The formula for these capsules is presented in Table I. The dissolution behavior of these capsules was evaluated by the method previously discussed, using rotating paddles, 100 rpm, 900 ml pH 6.0 phosphate buffer at 37 degrees C. The average % azithromycin dissolved at 15 minutes was 25%, and at 30 minutes was 76%.

The effect of feeding on azithromycin bioavailability was determined as follows. Eleven healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast (food and fluid) of 12 hr. The dose was swallowed with 150 ml water, and a further 150 ml water was taken at 1 hr post-dosing. On the other occasion, the subjects consumed a meal consisting of milk, bread and butter, bacon, 2 fried eggs, and coffee. The dose was administered with 150 ml water within 30 minutes of completion of the meal. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition. The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.22, with lower and upper 90% confidence levels of 0.06 and 0.84, respectively.

TABLE I

Formulation of 250 mg Azithromycin Capsules. Prepared in #0 white opaque locking type capsules.

INGREDIENT	MG/CAPSULE
Azithromycin*	263.72
Lactose, anhydrous	149.88
Corn starch, hydrous	47.0
Magnesium stearate/Sodium lauryl sulfate (90/10)	9.40
TOTAL	470.0

*Based on a bulk potency of 94.8%; Non-stoichiometric hydrate.

EXAMPLE 2

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolved more quickly than the capsules of Example 1.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 97% of the encapsulated azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces whole-fat milk. The oral doses were administered with 250 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on azithromycin oral bioavailability. The average AUCfed/AUCfasted was 0.80, with lower and upper 90% confidence levels of 0.67 and 0.96, respectively.

TABLE II

Formula for Azithromycin capsules. This formula was prepared as a dry granulation and was loaded into #0 opaque locking capsules.

INGREDIENT	MG/CAPSULE
Azithromycin Dihydrate*	262.05
Lactose, anhydrous	151.55
Corn starch, hydrous	47.00
Magnesium stearate/Sodium lauryl sulfate	9.40
TOTAL	470.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.

EXAMPLE 3

This example is comparative and demonstrates the effect of a light breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolves quickly.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 99% of the encapsulated azithromycin was dissolved.

The effect of a light (Continental) breakfast on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (4×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after consumption of a light breakfast consisting of two rolls with butter and jam and Ca. 300 ml of coffee or tea with milk. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 46.5 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the

area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.71, with lower and upper 90% confidence levels of 0.53 and 0.95, respectively.

EXAMPLE 4

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

Azithromycin tablets were prepared according to the formula given in Table III. Dissolution evaluation was carried out as in Example 1. At 30 minutes, 100% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.97, with lower and upper 90% confidence levels of 0.82 and 1.13, respectively.

TABLE III

Formula for azithromycin film coated tablets. This formula was compressed to form a 0.262" × 0.5312" modified capsular, upper engraved "Pfizer", lower scored, tablet, and was coated with "pink Opadry".

INGREDIENT	WEIGHT (MG/UNIT)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, anhydrous	138.84
Sodium croscarmellose***	9.00
Magnesium stearate/Sodium lauryl sulfate (90/10)	13.11
Pink Opadry II##	18.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains lactose, hydroxypropyl methylcellulose, titanium dioxide, triacetin, and D&C Red No. 30 Aluminum Lake.

EXAMPLE 5

This example demonstrates the effect of a Japanese meal on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

A tablet dosage form of azithromycin was prepared according to the formula described in Table IV. Dissolution of this dosage form was evaluated as in Example 1. In 15 minutes, 100% of the azithromycin dose was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Eight healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed 30 minutes after consumption of a Japanese meal consisting of rice, miso soup, fried egg, seaweed, spinach, and pickles. The oral doses were administered with 200 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.00, with lower and upper 90% confidence levels of 0.87 and 1.15, respectively.

TABLE IV

Azithromycin film-coated tablet formula. Capsular plain white film-coated tablets (0.262" × 0.5312") were compressed and then coated with "White Opadry"and "Clear Opadry".

INGREDIENT	WEIGHT (MG/TABLET)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, Anhydrous	138.84
Sodium croscarmellose***	9.00
White Opadry##	12.825
Clear Opadry###	0.675
Magnesium Stearate/ Sodium Lauryl Sulfate (90/10)	13.11

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains hydroxypropyl methylcellulose, titanium dioxide, polyethyleneglycol, and polysorbate 80.
###Contains hydroxypropyl methylcellulose and polyethyleneglycol.

EXAMPLE 6

This example compares the effects of a high fat breakfast and a low fat breakfast on systemic exposure of azithromycin dosed in a "Powder for Oral Suspension" dosage form.

An azithromycin "Powder for Oral Suspension" was prepared according to the formula in Table V. This formula was designed to wet and disperse quickly when reconstituted with an aqueous vehicle. Dissolution of this suspension was evaluated as described in the "Detailed Description". In 15 minutes 97% of the azithromycin dose dissolved; in 30 minutes 99.6% of the azithromycin dose dissolved.

The effect of a high fat meal and a low fat meal on azithromycin bioavailability from this suspension dosage form was determined as follows. Six healthy male human volunteers were orally dosed with 500 mg azithromycin (12.5 ml of a 40 mg/ml oral suspension), on each of 3 occasions. On one occasion, the subjects were dosed after an overnight fast of 10–12 hr. On another occasion the subjects were dosed after consumption of a high fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. On the third occasion, the subjects were dosed after consumption of a low fat meal consisting of one ounce of Cheerios (registered trademark of

General Mills Inc.) cereal and eight ounces of whole milk. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. For the high fat meal, the average AUCfed/AUCfasted was 1.01, with lower and upper 90% confidence levels of 0.79 and 1.28, respectively. For the low fat meal, the average AUCfed/AUCfasted was 1.04, with lower and upper 90% confidence levels of 0.82 and 1.33, respectively.

TABLE V

Formula for azithromycin "Powder for Oral Suspension". To reconstitute this formulation, 0.52 ml water was added per gm dry formulation.

INGREDIENT	WEIGHT (MG/BOTTLE)
Azithromycin dihydrate*	838.57
Sucrose	15487.74
Sodium phosphate tribasic, anhydrous	70.01
Hydroxypropylcellulose (Klucel-EF)	26.62
Xanthan gum (Keltrol)	26.62
FD&C Red #40	0.67
Spray Dried Cherry #11929	59.94
Art. Creme de Vanilla #11489	133.28
S.D. Art. Banana #15223	99.96
TOTAL	16743.41

*Based on a bulk potency of 95.4%.

EXAMPLE 7

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a "Single Dose Packet" (sachet) dosage form.

A "Single Dose Packet" (sachet) dosage form of azithromycin was prepared according to the formula described in Table VI. Dissolution of this dosage form was evaluated as described in the "Detailed Description" above. In 15 minutes, 99% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this sachet dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (1 gm sachet), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast of at least 12 hr, and on the other occasion the subjects were dosed after consumption of a high-fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and with two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.12, with lower and upper 90% confidence levels of 0.99 and 1.27.

TABLE VI

Formula for azithromycin "Unit Dose Packet" dosage form. This blend was prepared, and filled into 3.25" × 4" white paper/aluminum/polyethylene laminate sachets. To reconstitute for dosing, the contents of a sachet is added to 60 ml water, and stirred well.

INGREDIENT	WEIGHT (GM/UNIT)
Azithromycin dihydrate*	1.048
Sucrose	9.707
Sodium phosphate tribasic, anhydrous	0.088
Colloidal silicon dioxide	0.055
Spray Dried art. cherry #11929	0.038
Spray Dried art. banana #15223	0.064
TOTAL	11.000

*Equivalent to 1 gm azithromycin, based on a bulk potency of 95.4% for azithromycin dihydrate.

EXAMPLE 8

Azithromycin tablets of this invention were prepared at 150, 200, 250, 300, 500, and 600 mg dosage strengths. Tablet cores were prepared by wet granulation of all tablet core ingredients (except magnesium stearate/sodium lauryl sulfate). The dried granules were blended with the lubricant mixture magnesium stearate/sodium lauryl sulfate, followed by tableting on a tablet press. Tablets were coated with an aqueous film coat comprising colored and/or clear Opadry. These tablet formulations do not exhibit an adverse food effect. Tablet formulations were as described in Table VII.

TABLE VII

Examples of azithromycin tablet formulations which do not exhibit a food effect.

	WEIGHT (MG/TABLET)					
Component	150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
Azithromycin dihydrate*	157.23	209.613	262.05	314.46	524.10	628.93
Pregelatinized starch**	16.20	21.60	27.00	32.40	54.00	64.80
Calcium phosphate dibasic, anhydrous	83.305	111.01	138.84	166.61	277.68	333.21
Sodium croscarmellose#	5.400	7.200	9.00	10.80	18.00	21.60

TABLE VII-continued

Examples of azithromycin tablet formulations which do not exhibit a food effect.

Component	WEIGHT (MG/TABLET) 150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
Magnesium stearate/ Sodium lauryl sulfate (90/10)	7.865	10.486	13.11	15.73	26.22	31.46
Opadry@	8.1	10.8	13.5	16.2	27.0	32.4
TOTAL	278.1	370.8	463.5	556.2	927.0	1,112.4

*Based on a theoretical potency of 95.4%.
**Starch 1500.
#e.g. Ac-Di-Sol.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifier, and lakes.

EXAMPLE 9

Additional tablet formulations of azithromycin (250 mg) are prepared which do not exhibit an adverse food effect and are described in Table VIII. The diluent in these formulations (calcium phosphate dibasic, anhydrous) may be substituted by calcium phosphate dibasic dihydrate, microcrystalline cellulose, lactose NF/BP/EP/JP, or other appropriate diluent. The lubricant in these tablets (magnesium stearate/sodium lauryl sulfate, 90/10) may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the calcium phosphate/pregelatinized starch ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance and serves to differentiate strengths. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies may be obtained by maintaining the approximate azithromycin/excipient ratios described in Table VIII, and increasing or decreasing total tablet weight.

TABLE VIII

Examples of azithromycin tablet formulations (250 mg) which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	262.05	262.05	262.05
Pregelatinized starch	50.0	13.9	50.0
Calcium phosphate dibasic, anh.	115.84	140.94	104.84
Sodium croscarmellose	9.0	20.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.50	13.50	13.50
TOTAL	463.5	463.5	463.5

@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

EXAMPLE 10

Further 250 mg azithromycin tablet formulations are prepared which do not exhibit an adverse food effect and are presented in Tables IX and X. In these formulations, maize starch, sodium starch glycolate, and crosslinked polyvinylpyrrolidone serve as disintegrants. Calcium phosphate dibasic, lactose NF/BP/EP, and microcrystalline cellulose serve as diluents.

Magnesium stearate/sodium lauryl sulfate serves as a lubricant. Magnesium stearate/sodium lauryl sulfate may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the diluent/disintegrant ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies are obtained by maintaining the approximate azithromycin/excipient ratios described in Tables IX and X, and increasing or decreasing total tablet weight. These formulas are illustrative, and substitutions of other disintegrants, diluents, and lubricants are possible, as known in the art.

TABLE IX

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 4	FORMULATION 5	FORMULATION 6
Azithromycin dihydrate†	262.05	262.05	262.05
Maize starch*	13.9	27.0	50.0
Calcium phosphate, dibasic** OR Lactose NF/BP/EP/JP OR Microcrystalline cellulose	151.94	138.84	115.84
Sodium starch glycolate# OR Crosslinked polyvinylpyrrolidone##	9.0	9.0	9.0

TABLE IX-continued

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 4	FORMULATION 5	FORMULATION 6
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

†Equivalent to 250 mg azithromycin.
*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
#e.g. Explotab or Primojel
##e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

TABLE X

Examples of azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 7	FORMULATION 8	FORMULATION 9
Azithromycin dihydrate†	262.05	262.05	262.05
Maize starch*	13.9	27.0	27.0
Calcium phosphate, dibasic** OR Lactose NF/BP/EP/JP OR Microcrystalline cellulose	140.94	144.84	127.84
Sodium starch glycolate# OR Crosslinked polyvinylpyrrolidone##	20.0	3.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
#e.g. Explotab or Primojel
##e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.
†Equivalent to 250 mg azithromycin.

EXAMPLE 11

The "Powder for Oral Suspension" formulation described in Table XI was prepared. This formulation does not exhibit an adverse food effect.

TABLE XI

A formulation for azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/GM)
Azithromycin dihydrate	47.97
Sucrose NF	579.71
Sorbitol, crystalline, powder, NF/FCC	289.86
Sodium carbonate, anhydrous, NF	18.84
Sodium benzoate, NF/FCC	4.35
Tragacanth gum powder, NF	14.49
Titanium dioxide USP	14.49
Colloidal silicon dioxide, NF	1.45
Aminoacetic acid (glycine) USP	5.80
Spray-dried Art. Strawberry #22653	15.26
Tropical apple punch #26508	7.63
Spray-dried peppermint stick #15634	0.15
TOTAL	1000.00

EXAMPLE 12

Azithromycin "Powder for Oral Suspension" formulations are prepared as illustrated in Tables XII and XIII. The unit potency of these formulations is 600 mg azithromycin/bottle, and the use potency after constitution with water is 40 mg/ml. To constitute, 0.52 ml water is added per gm of blend. 9 mL water and 16.74 gm blend produce approximately 20 ml suspension. These formulations include 200 mg Azithromycin/bottle overfill. The listed "flavor system" may be freely substituted with other flavors which provide a pleasant taste and are stable at pH 10 over the shelf-life of the constituted suspension (approximately 5 days). The dye may also be freely substituted. The formulations in this Example are illustrative, and not limiting. These formulations do not exhibit an adverse food effect.

TABLE XII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE) FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	838.57	838.57	838.57
Sucrose NF	15487.74	15370.54	15487.74
Sodium phosphate tribasic anhydrous	70.01	70.01	70.01
Hydroxypropyl-cellulose	26.62	26.62	0
Xanthan gum	26.62	26.62	0
Sodium carboxy-methylcellulose	0	0	53.24
Colloidal silicon dioxide	0	16.74	0
Glycine	0	100.46	0
Spray-dried cherry #11929	59.94	59.94	59.94
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

TABLE XIII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE FORMULATION 4	FORMULATION 5	FORMULATION 6
Azithromycin dihydrate	838.57	838.57	838.57
Sorbitol	15138.55	7743.87	7656.37
Sucrose NF	0	7743.87	7656.37
Sodium carbonate, anhydrous, NF	302.00	0	150.00
Sodium phosphate tribasic anhydrous	0	70.01	35.00
Hydroxypropyl-cellulose	0	26.62	17.75
Xanthan gum	0	26.62	17.75
Sodium carboxy-methylcellulose	53.24	0	17.75
Colloidal silicon dioxide	16.74	0	10.00
Glycine	100.46	0	50.00
Spray-dried cherry #11929	59.94	59.94	59.94
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

EXAMPLE 14

The following formulations of unit dose packets of azithromycin are prepared as being exemplary, not limiting, of the invention (Tables XIV and XV). The flavor system for these dosage forms may be freely substituted with any flavor system which provides a pleasant taste when the contents of the packet are reconstituted in water or an aqueous beverage. When constituted in water or an aqueous beverage, these dosage forms do not exhibit an adverse food effect.

TABLE XIV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	9.707	9.707	5.0
sorbitol	0	0	0
sodium phosphate tribasic, anhydrous	0.04	0.2	0.088
sodium carbonate, anhydrous	0	0	0
glycine	0	0	0
colloidal silicon dioxide	0.022	0.22	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray-dried art. banana #15223	0.064	0.064	0.064

TABLE XV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	0	4.85	4.85
sorbitol	9.707	4.85	4.85
sodium phosphate tribasic, anhydrous	0.088	0.088	0.044
sodium carbonate, anhydrous	0	0	0.022
glycine	0	0	0.022
colloidal silicon dioxide	0.055	0.055	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray-dried art. banana #15223	0.064	0.064	0.064

What is claimed is:

1. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

2. A dosage form as defined in claim **1**, wherein said mammal is a human.

3. A dosage form as defined in claim **1**, further comprising a flavoring agent.

4. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

5. A dosage form as defined in claim **4**, wherein said mammal is a human.

6. A dosage form as defined in claim **4**, further comprising a flavoring agent.

7. A dosage form as defined in claim **6**, wherein said flavoring agent is a flavor system consisting of cherry, vanilla, and banana.

8. A dosage form as defined in claim **4**, in the form of a suspension made from said powder.

9. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which

comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

10. A dosage form as defined in claim **9**, wherein said mammal is a human.

11. A dosage form as defined in claim **9**, further comprising an anhydrous buffer.

12. A dosage form as defined in claim **9**, wherein said dispersing agent is colloidal silicon dioxide.

13. A dosage form as defined in claim **9**, in the form of a suspension made from said unit dose packet.

14. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

15. A dosage form as defined in claim **14**, wherein said mammal is a human.

16. A dosage form as defined in claim **14**, further comprising a flavoring agent.

17. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing an anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

18. A dosage form as defined in claim **17**, wherein said mammal is a human.

19. A dosage form as defined in claim **17**, further comprising a flavoring agent.

20. A dosage form as defined in claim **19**, wherein said flavoring agent is a flavoring system consisting of cherry, vanilla, and banana.

21. A dosage form as defined in claim **17**, in the form of a suspension made from said powder.

22. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

23. A dosage form as defined in claim **22**, wherein said mammal is a human.

24. A dosage form as defined in claim **22**, further comprising an anhydrous buffer.

25. A dosage form as defined in claim **22**, wherein said dispersing agent is colloidal silicon dioxide.

26. A dosage form as defined in claim **22**, in the form of a suspension made from said unit dose packet.

27. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
6.0% pregelatinized starch;
30.9% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

28. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
25.7% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

29. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
3.1% pregelatinized starch;
31.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

30. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
23.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

31. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

32. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

33. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
11.1% maize starch;
25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

34. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

35. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;

32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

36. A dosage form as defined in claim **1**, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

37. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
trace coloring; and
1.8% flavoring.

38. A dosage form as defined in claim **4**, comprising:
4.8% azithromycin dihydrate;
58.0% sucrose;
29.0% sorbitol;
1.9% anhydrous sodium carbonate;
0.4% sodium benzoate;
1.5% tragacanth gum powder;
1.5% titanium dioxide;
1.15% colloidal silicon dioxide;
0.6% glycine; and
2.3% flavoring.

39. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
91.8% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

40. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.3% sodium carboxymethylcellulose;
trace coloring; and
1.8% flavoring.

41. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
90.4% sorbitol;
1.8% anhydrous sodium carbonate;
0.3% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

42. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
46.3% sorbitol;
46.3% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylmethylcellulose;
0.2% xanthan gum; and
trace coloring
1.8% flavoring.

43. A dosage form as defined in claim **4**, comprising:
5.0% azithromycin dihydrate;
45.7% sucrose;
45.7% sorbitol;
0.9% anhydrous sodium carbonate;
0.2% anhydrous tribasic sodium phosphate;
0.1% hydroxypropylmethylcellulose;
0.1% xanthan gum;
0.1% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.3% glycine;
trace coloring; and
1.8% flavoring.

44. A dosage form as defined in claim **9**, comprising:
9.5% azithromycin dihydrate;
88.2% sucrose;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

45. A dosage form as defined in claim **9**, comprising:
9.5% azithromycin dihydrate;
88.2% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

46. A dosage form as defined in claim **9**, comprising:
9.6% azithromycin dihydrate;
88.9% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% colloidal silicon dioxide; and
0.9% flavoring.

47. A dosage form as defined in claim **9**, comprising:
9.3% azithromycin dihydrate;
86.1% sucrose;
1.8% anhydrous tribasic sodium phosphate;
2.0% colloidal silicon dioxide; and
0.9% flavoring.

48. A dosage form as defined in claim **9**, comprising:
16.7% azithromycin dihydrate;
79.5% sucrose;
1.4% anhydrous tribasic sodium phosphate;
0.9% colloidal silicon dioxide; and
1.6% flavoring.

49. A dosage form as defined in claim **9**, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and

0.9% flavoring.

50. A dosage form as defined in claim **9**, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.4% anhydrous tribasic sodium phosphate;

0.2% anhydrous sodium carbonate;

0.2% glycine;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

51. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

6.0% pregelatinized starch;

30.9% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% lubricant.

52. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

11.1% pregelatinized starch;

25.7% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% lubricant.

53. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

3.1% pregelatinized starch;

31.3% anhydrous dibasic calcium phosphate;

4.4% sodium croscarmellose; and

2.9% lubricant.

54. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

11.1% pregelatinized starch;

23.3% anhydrous dibasic calcium phosphate;

4.4% sodium croscarmellose; and

2.9% lubricant.

55. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

3.1% maize starch;

33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

56. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

57. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

11.1% maize starch;

25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

58. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

3.1% maize starch;

31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

59. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

60. A dosage form as defined in claim **14**, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

61. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

92.5% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylcellulose;

0.2% xanthan gum;

trace coloring; and

1.8% flavoring.

62. A dosage form as defined in claim **17**, comprising:

4.8% azithromycin dihydrate;

58.0% sucrose;

29.0% sorbitol;

1.9% anhydrous sodium carbonate;

0.4% sodium benzoate;

1.5% tragacanth gum powder;

1.5% titanium dioxide;

1.15% colloidal silicon dioxide;

0.6% glycine; and

2.3% flavoring.

63. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

91.8% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylcellulose;

0.2% xanthan gum;

0.1% colloidal silicon dioxide;

0.6% glycine;

trace coloring; and

1.8% flavoring.

64. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

92.5% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.3% sodium carboxymethylcellulose;

trace coloring; and

1.8% flavoring.

65. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

90.4% sorbitol;

1.8% anhydrous sodium carbonate;

0.3% sodium carboxymethylcellulose;

0.1% colloidal silicon dioxide;

0.6% glycine;

trace coloring; and

1.8% flavoring.

66. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

46.3% sorbitol;

46.3% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylmethylcellulose;

0.2% xanthan gum; and

trace coloring

1.8% flavoring.

67. A dosage form as defined in claim **17**, comprising:

5.0% azithromycin dihydrate;

45.7% sucrose;

45.7% sorbitol;

0.9% anhydrous sodium carbonate;

0.2% anhydrous tribasic sodium phosphate;

0.1% hydroxypropylmethylcellulose;

0.1% xanthan gum;

0.1% sodium carboxymethylcellulose;

0.1% colloidal silicon dioxide;

0.3% glycine;

trace coloring; and

1.8% flavoring.

68. A dosage form as defined in claim **22**, comprising:

9.5% azithromycin dihydrate;

88.2% sucrose;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

69. A dosage form as defined in claim **22**, comprising:

9.5% azithromycin dihydrate;

88.2% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

70. A dosage form as defined in claim **22**, comprising:

9.6% azithromycin dihydrate;

88.9% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% colloidal silicon dioxide; and

0.9% flavoring.

71. A dosage form as defined in claim **22**, comprising:

9.3% azithromycin dihydrate;

86.1% sucrose;

1.8% anhydrous tribasic sodium phosphate;

2.0% colloidal silicon dioxide; and

0.9% flavoring.

72. A dosage form as defined in claim **22**, comprising:

16.7% azithromycin dihydrate;

79.5% sucrose;

1.4% anhydrous tribasic sodium phosphate;

0.9% colloidal silicon dioxide; and

1.6% flavoring.

73. A dosage form as defined in claim **22**, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

74. A dosage form as defined in claim **22**, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.4% anhydrous tribasic sodium phosphate;

0.2% anhydrous sodium carbonate;

0.2% glycine;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

75. A therapeutic package, comprising

a container,

an oral dosage form of azithromycin which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or

(b) a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75,

and, associated with said package, written matter non-limited as to whether the dosage form can be taken with or without food.

76. A therapeutic package as defined in claim **75**, wherein said dosage form is in the form of a tablet.

77. A therapeutic package as defined in claim **75**, wherein said dosage form is in the form of a powder for oral suspension.

78. A therapeutic package as defined in claim **77**, wherein said dosage form is in the form of a suspension made from said powder.

79. A therapeutic package as defined in claim **75**, wherein said dosage form is in the form of a unit dose packet.

80. A therapeutic package as defined in claim **79**, wherein said dosage form is in the form of a suspension made from said unit dose packet.

81. A method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or

(b) a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

82. A method as defined in claim 81, wherein said mammal is a human.

83. A method as defined in claim 82, wherein said dosage form exhibits a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

84. A method as defined in claim 82, wherein said dosage form is in the form of a tablet.

85. A method as defined in claim 82, wherein said dosage form is in the form of a powder for oral suspension.

86. A method as defined in claim 85, wherein said dosage form is in the form of a suspension made from said powder.

87. A method as defined in claim 82, wherein said dosage form is in the form of a unit dose packet.

88. Method as defined in claim 87, wherein said dosage form is in the form of a suspension made from said unit dose packet.

89. A method as defined in claim 83, wherein said dosage form is in the form of a tablet.

90. A method as defined in claim 89, wherein said dosage form is in the form of a powder for oral suspension.

91. A method as defined in claim 90, wherein said dosage form is in the form of a suspension made from said powder.

92. A method as defined in claim 83, wherein said dosage form is in the form of a unit dose packet.

93. A method as defined in claim 92, wherein said dosage form is in the form of a suspension made from said unit dose packet.

94. A package as defined in claim 75, wherein said dosage form exhibits a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

95. A package as defined in claim 94, wherein said dosage form is in the form of a tablet.

96. A package as defined in claim 94 wherein said dosage form is in the form of a powder for oral suspension.

97. A package as defined in claim 96, wherein said dosage form is in the form of a suspension made from said powder.

98. A package as defined in claim 94, wherein said dosage form is in the form of a unit dose packet.

99. A package as defined in claim 98, wherein said dosage form is in the form of a suspension made from said unit dose packet.

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EXHIBIT G

Search Result List							
Court	**Docket Number**	**Description**	**Participant**	**Filed**	**Date Retrieved**	**Active or Closed**	**Identification**
U.S. District - Delaware	1:98cv406	Glaxo Wellcome Inc v. Teva Pharmaceuticals	-	07/14/1998	08/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:00cv35	Merck & Co Inc v. Teva Pharm USA Inc, et al	-	01/19/2000	07/27/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:00cv466	Bayer AG, et al v. Biovail Corporation, et al	-	05/08/2000	02/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:01cv48	Merck & Co Inc v. Teva Pharmaceuticals	-	01/25/2001	08/29/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:01cv675	Merck & Co Inc v. Teva Pharmaceuticals	-	10/04/2001	02/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:01cv728	Merck & Co Inc v. Teva Pharmaceuticals	-	11/06/2001	02/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:02cv219	Glaxo Group Limited, et al v. Teva Pharmaceuticals, et al	-	03/22/2002	03/03/2006	Closed	NOS : (830) Patent
U.S. District - Delaware	1:02cv332	Novo Nordisk Pharm, et al v. Bio-Technology Gen, et al	-	04/30/2002	01/20/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:02cv1377	Merck & Co Inc v. Teva Pharmaceuticals	-	08/13/2002	02/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:02cv1512	Abbott Laboratories, et al v. Teva Pharmaceuticals	-	10/04/2002	03/03/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:03cv773	Merck & Co Inc, et al v. Teva Pharmaceuticals	-	08/04/2003	06/23/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:03cv808	Teva Pharmaceuticals, et al v. Pharmaceutical Inc, et al	-	08/14/2003	02/02/2005	Closed	NOS : (830) Patent
U.S. District - Delaware	1:03cv847	Abbott Laboratories, et al v. Teva Pharmaceuticals	-	08/29/2003	03/01/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:03cv858	Glaxo Group Limited, et al v. Teva Pharm USA Inc, et al	-	09/04/2003	03/03/2006	Closed	NOS : (830) Patent
U.S. District - Delaware	1:03cv1039	Glaxo Group Limited, et al v. Teva Pharmaceuticals, et al	-	11/03/2003	03/03/2006	Closed	NOS : (830) Patent
U.S. District - Delaware	1:04cv20	Glaxo Group Limited, et al v. Teva Pharmaceuticals, et al	-	01/09/2004	03/03/2006	Closed	NOS : (830) Patent
U.S. District - Delaware	1:04cv47	Abbott Laboratories, et al v. Teva Pharmaceuticals	-	01/22/2004	01/19/2006	Active	NOS : (830) Patent

U.S. District - Delaware	1:04cv171	Glaxo Group Limited v. Teva Pharma USA Inc, et al	-	03/18/2004	02/28/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:04cv884	Ferring BV v. Teva Pharmaceuticals, et al	-	07/20/2004	02/28/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:04cv939	Merck & Co Inc v. Teva Pharmaceuticals	-	08/13/2004	03/01/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:04cv940	Procter & Gamble Co v. Teva Pharmaceuticals	-	08/13/2004	03/03/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:05cv197	Smith Kline & French Laboratories Limited et al v. Teva Pharmaceuticals USA Inc	-	04/06/2005	03/03/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:05cv336	Item Development AB et al v. Sicor Inc et al	-	05/26/2005	02/28/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:05cv337	King Pharmaceuticals Research and Development, Inc et al v. Sicor Inc Et A	-	05/26/2005	02/28/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:05cv356	In Re: '318 Patent Infringement Litigation	-	06/03/2005	03/03/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:05cv562	King Pharmaceuticals Inc et al v. Teva Pharmaceuticals USA Inc	-	08/03/2005	03/03/2006	Closed	NOS : (830) Patent
U.S. District - Delaware	1:06cv33	Takeda Pharmaceutical Company Ltd et al v. Teva Pharmaceuticals USA Inc	-	01/17/2006	02/28/2006	Active	NOS : (830) Patent
U.S. District - Delaware	1:06cv89	Pfizer Inc v. Teva Pharmaceuticals USA et al	-	02/08/2006	02/28/2006	Active	NOS : (830) Patent

Total number of results: 28

Search Title Untitled Search 3/3/2006 (2)

Client Matter Code 121*841

U.S. District Courts (Civil)

Courts United States District Courts (Civil) - Delaware

Litigants Teva Plaintiff,Defendant,Other

Case Types Civil

Case Status ALL